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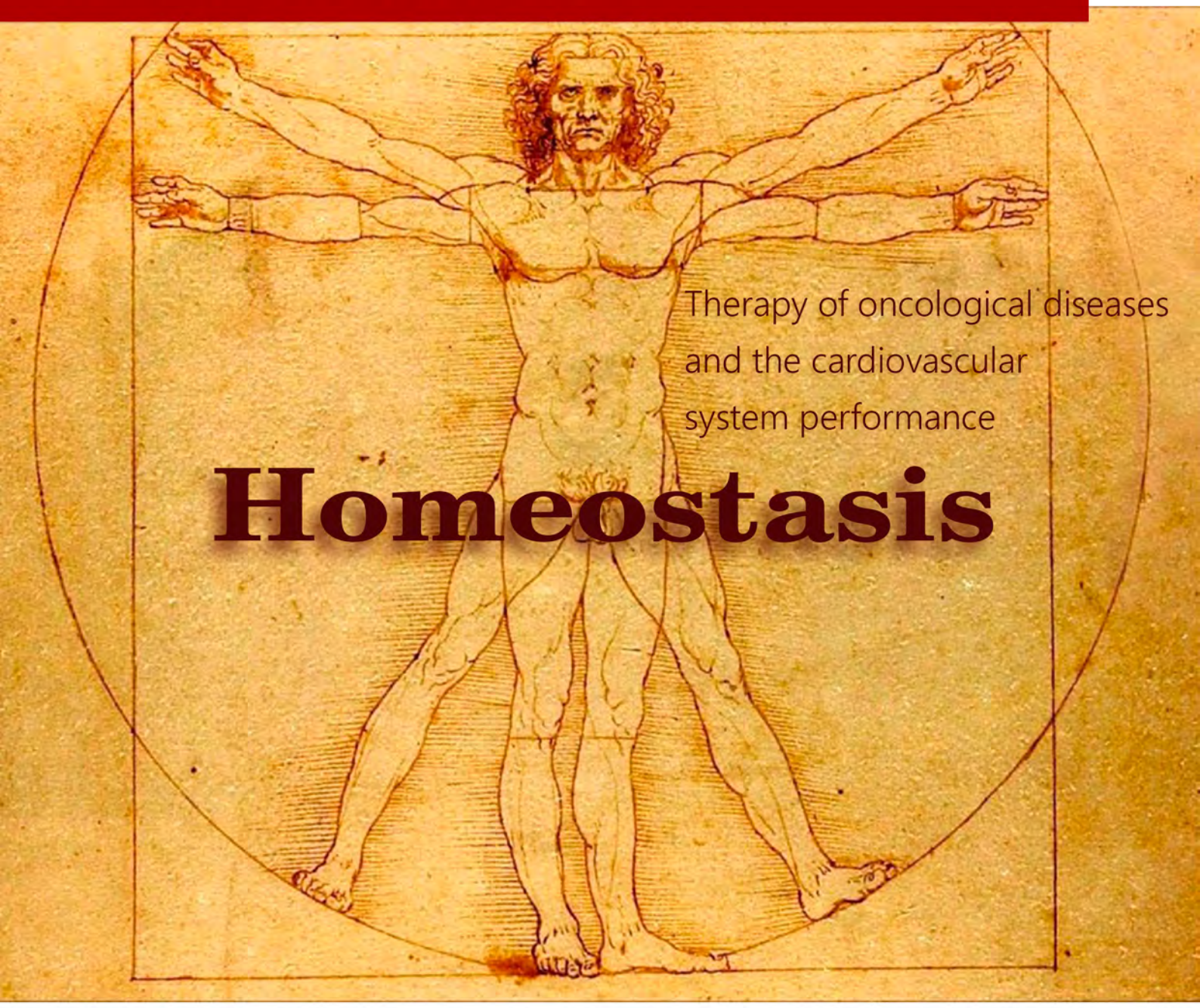

Therapy of oncological diseases and the cardiovascular system performance

Homeostasis

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EDITORIAL

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***Maria A. Ukolova*,**

prominent Russian researcher, Doctor of Medical Sciences, Professor

We remember in October 2021 the 115th anniversary of the birth of Maria A. Ukolova, the prominent Russian researcher, Doctor of Medical Sciences, Professor, First Deputy Director for Science at the Rostov-on-Don Research Institute of Oncology (RRIO), the originator of new research areas, who was the head of the experimental department at the above Institute, the founder of the first scientific school for accompanying magnetotherapy of tumors in Russia, the co-author of the world-class-level discovery "Pattern of development of qualitatively differing general unspecific adaptational reactions of the organism" (Scientific Discovery Registration Certificate No. 158 issued by the Committee on Inventions and Discoveries at the Council of Ministers of the USSR, Moscow, 1975).

For more than 50 years of her outstanding research work at the RRIO, she made a great contribution to the solution to the topical challenge: the identification and definition of the complex relationship between the tumor and the human organism. In 1960, M.A. Ukolova published her first research report in the USSR, where she treated actions and effects produced by various magnetic fields on the growth of malignant tumors in an experiment.

The great multifaceted talent M.Ukolova possessed was recognized by her students: first of all by Lyubov Garkavi, Yuri Bordyushkov, Elena Kvakina, who became prominent scientists having a worldwide reputation, whose fundamental works formed the basis of the theory of adaptational reactions as a groundwork for accompanying cancer therapy.

The close cooperation of Maria A. Ukolova with A.S. Presman, Yu.A. Kholodov, N.V. Vasiliev, the outstanding Russian scientists, the founders of magnetobiology, as well as with the biggest scientific schools in Moscow, Pushchino-on-Oka, St. Petersburg, Tomsk, Novosibirsk, Samara, Riga, Vitebsk and Rostov-on-Don made it possible to consolidate the efforts in research at that time, in the 60s, and move forward under the present-day conditions to promote development of advanced science-intensive technologies.

The activation electromagnetotherapy of tumors is a unique product that has never been used before in the world, and among the pioneers of this original treatment technique are prominent researchers and passionate scientists: Maria A. Ukolova, Lyubov H. Garkavi, Elena B. Kvakina and their followers. It should be stressed that we very much appreciate the continual personal endeavors to maintain and refine this scientific approach that is made by Oleg I. Kit, Director General of the Rostov National Medical Research Center of Oncology at the Ministry of Health of Russia, Doctor of Medical Sciences, Professor, Corresponding Member of the Russian Academy of Sciences, who creates all the optimal conditions for the development of the theoretical concepts aimed at further experimental research on actions and effects produced by magnetic fields applicable to tumor treatment, who makes a major effort to equipping with new instrumentation the research labs at the above National Center and who provides invaluable support to this priority scientific area, following the conceptual philosophy originated by Maria A. Ukolova.

At present, the leadership position in the above innovative promising research area has been taken by Professor Elena M. Frantsiyants, Deputy Director General for Research, Doctor of Biological Sciences, the brilliant theorist and experimenter, who is responsible for further studies of pathogenesis of malignant tumors at the above Rostov Cancer Center because this research field is capable of discovering new horizons in science.

Alla I. Shikhlyarova

Doctor of Biological Sciences, Professor
Honored Healthcare Employer
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Laboratory for Studies of Pathogenesis of Malignant Tumors
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the Ministry of Health of Russian Federation

EDITORIAL

Study of the effect made by interval hypoxic training on cardiac metabolism and hemodynamics

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Imprint

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In this study, the Go2Altitude hypoxicator produced by the Australian company BiotechMed was used [1]. A 60-year-old male patient, height 182 cm, weight 95 kg, was fed in alternating mode, 5 minutes / 3 minutes, a mixture of oxygen 12% and nitrogen 88% through a mask, with room air (approximately 20.9% oxygen and 79.1% nitrogen) during the 45-minute session. Figure 1 given herein shows the ECG and rheogram curves recorded before and after exposure to interval hypoxic training (IHT). Observed is stable amplitude of the rheogram, which indicates the balance between the systemic and pulmonary circulation. Secondly, the Тк-Uн segment has been normalized.

The data given in our Table 1 herein show an effective impact of hypoxia on the parameters of the cardiovascular system performance, namely:

1. An increase in the phosphocreatine (PCr) concentration in the heart muscle fiber cells. This contributes to an increase in the reserves of the instantaneous energy consumption in critical cases, which indicates an increase in the heart performance efficiency (reflected in fatigue mitigation).

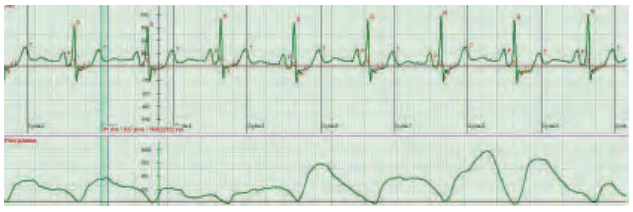
2. During the orthostatic test, the hemodynamic indicator, stroke volume SV, shows the restoration of changes in the distribution of pressure throughout the body, namely, that when the body moves from a horizontal to a vertical position, the normal conditions of the difference in blood pressure in the aorta and the peripheral vessels are restored, which improves the tolerability to physical loading [2, 3].

3. The coronary blood flow is significantly restored.

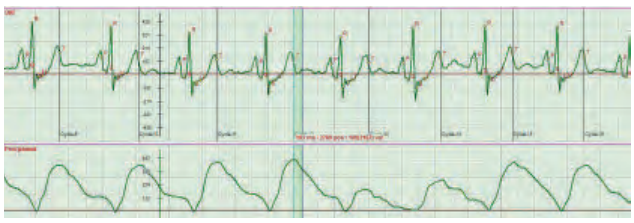
4. We observe a transition to a better type of the adaptational reaction: the reaction of stress (rS) is eliminated with turning into the reaction of training (rT) [4].

As a result, the system indicator, the stress index (SI) value [5-7] significantly improves that indicates the correction of the coronary blood flow and better conditioning of the organism in general.

These studies show the possibility of regulating the complex coronary processes with the use of the interval hypoxic training.



a) Before hypoxia



b) After hypoxia

Figure 1. ECG and Rheograms recorded before and after hypoxia

Table 1

The effects of hypoxia on the cardiac metabolism and hemodynamics

No.	Date	Stage	O_2 0,5...0,55; 0,6...0,65; 0,7...0,85) arb.u.		Lactate (3...7) arb.u.		PCr (2...4) arb.u.		RV1 (62%) ejection fraction		(150...300) Type of adaptational reaction	
			l	s	l	s	l	s	l	s	l	s
1	June, 20, 2017	Before using hypoxicator	0.57	0.47	3.76	4.73	6.9	8.87	59	59	1651 Calm activation	474 Str.
2		After using hypoxicator	0.50	0.52	4.49	4.12	10.4	11.9	59	59	452 Calm activation	458 Training

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ORIGINAL RESEARCH

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Present-day tendencies in accompanying therapy in cancer treatment: from theory of adaptational reactions to bio-information technologies translation

Oleg I. Kit, Alla I. Shikhlyarova*, GalinaV. Zhukova, Elena M. Frantsiyants, Irina V. Kaplieva, Marina A. Engibaryan, Liubov Yu. Vladimirova, Elena A. Sheiko, Natalia N. Popova, Ivan A. Popov, Dmitry P. Atmachidi, Stella M. Babieva, Elena V. Filatova, Mikhail S. Zinkovich, Yuliana S. Shatova

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Abstract

At present, to develop new, scientifically justified, technologies of an accompanying therapy to improve the oncological situation is a challenge to health care. A therapy to accompany a specific cancer treatment in case of a malignant process in an organism is dictated by the necessity to raise the nonspecific resistance of the organism in cancer patients. In this case, original methodological approaches to initiate the mechanisms of the nonspecific resistance have been developed on the basis of the theory of the adaptational reactions. Within the framework of the above theory, some concepts of relationship between the specific and nonspecific anti-tumor processes have been extensively developed that may be successfully applied to solving tasks of the National Health Care Program.

Aim. The aim hereof is to introduce the theoretical basics of the nonspecific adaptation regulation and control by a tumor-bearing organism into practice for an integrated treatment of malignant tumors with the use of the activation therapy technologies. **Materials and methods.** Our research work has involved clinical data on 1310 patients, who have been diagnosed with cancer of different localization: breast cancer (n = 170), cervical cancer (n = 60), lung cancer (n = 760), bladder cancer (n = 120), brain gliomas of high grade of malignancy and metastatic damage (n = 170) and extended colorectal cancer (n = 30) and who have completed their treatment at the National Medical Research Centre of Oncology of the Ministry of Health of the Russian Federation.

Results and Discussion. We have used at different stages of the cancer treatment some technologies of the accompanying therapy, designed and developed on the basis of the approaches and principles of adaptive responding by a human organism. The above line of attack has provided a time- and intensity-scheduled functional loading (some factors of the electromagnetic and pharmacological nature) under control over formation of the desired stable reactions of the anti-stressor type. Following the principles of the activation therapy, the designed programmable regimes of extra actions and exposures have resulted in improvement of immediate outcomes of the treatment of malignant tumors, raise in quality and prolongation of life in our cancer patients.

Keywords

Accompanying therapy, Cancer treatment, Activation therapy, Adaptation

Imprint

Oleg I. Kit, Alla I. Shikhlyarova*, Galina V. Zhukova, Elena M. Frantsiyants, Irina V. Kaplieva, Marina A. Engibaryan, Liubov Yu. Vladimirova, Elena A. Sheiko, Natalia N. Popova, Ivan A. Popov, Dmitry P. Atmachidi, Stella M. Babieva, Elena V. Filatova, Mikhail S. Zinkovich, Yuliana S. Shatova. Present-day tendencies in accompanying therapy in cancer treatment: from theory of adaptational reactions to bio-information technologies translation. Cardiometry; Issue 20; November 2021; p. 10-20; DOI: 10.18137/cardiometry.2021.20.1020; Available from: http://www.cardiometry.net/issues/no20-november-2021/Present-day-tendencies

Introduction

A great deal of the health care efforts and material costs used in oncology treatment are not sufficiently supported by the required comprehensive measures to provide prolonged anti-tumor effects, health recovery, an increase in healthy life span and a raise in life quality of cancer patients.

Leading Russian national experts in oncology think there is practically no "oncological rehabilitation service system" in Russia available, including methodological basics for its establishing [1, 2]. Therefore, it should be stated that the oncological patients, upon completion of their high-tech anti-tumor therapy, accompanied by some stressogenic effects, are really limited in their choice in sets of the offered systemic personalized recommendations for an eligible accompanying therapy, functional rehabilitation, prevention of recurrent cases

and metastasis, or (in most unfavorable cases) palliative care and a reduction of a paraneoplastic syndrome burden. In other words, despite the fact that there is a an immense experience in the specialized treatment of tumors, we observe in the circumstances a lack of theoretical and a practical readiness to control the natural mechanisms in a human organism responsible for an increase in the natural nonspecific resistance to the tumor appearance, whereas the above mentioned mechanisms are genetically predetermined and allocated by different levels of the system self-organization, beginning with the subcellular level and ending with the organism as a whole.

In order to overcome the incompleteness of the existing integrated anti-tumor treatment, new approaches are required, which are based on fundamental knowledge of laws of the system regulation and the integral adaptational processes responsible for the state of the nonspecific resistance in a human organism. It makes possible to consider the theory of general nonspecific adaptational reactions (AR) by a human organism, developed by Russian researchers L.Ch. Garkavi, E.B. Kvakina and M.A. Ukolova on the basis of their discovery of laws of how qualitatively different integral ARs are produced [3], including the widely known stress introduced by Hans Selye [4, 5], as the required scientific platform for an accompanying therapy and formation of the system of rehabilitation of oncological patients.

As a result from many years of the research work completed by the above scientists and devoted to the identification of the role of the adaptational reactions in the growth and regression of tumors, an original strategic approach has been elaborated in order to increase the nonspecific and anti-tumor resistance of a human organism and an original treatment technology has been developed, which has been referred to as the activation therapy, with establishing its strategy and tactics, exactly defining its basics and criteria for an assessment of the actual status of the organism and its systems and offering the required methodological recommendations [6-8].

The translation of the fundamental developments into clinical practice has shown that the activation therapy is effective as an accompanying treatment for patients with a malignant process of different tumor cell dissemination grades and various localizations [8, 9]. Moreover, using effects produced by low-intensity electromagnetic fields and low dosing of biologically active substances, applied according to certain specified algorithms of the activation therapy, we have demonstrated the possibility to enhance the effectiveness of anti-tumor chemotherapy drugs with reducing their dosage as well as to activate the mechanisms of the anti-tumor resistance in the early post-surgery period in most pronounced way that has substantially decreased a complication incidence and improved quality of life in this sort of patients [10-12].

By this means it should be noted that the revealed typological features of the anti-stressor ARs, the developed strategies and digital programmable regimes of exposures and actions, simple adequate criteria for an assessment of the current status of a human organism may be taken as the reference points to apply the effective methods of the rehabilitation of oncological patients both in time between the basic anti-tumor treatment courses and upon completion of the specialized major therapy, and in the latter case it may be offered via telemedicine options.

The aim of our research work is to bring the applications of the theoretical basics of the nonspecific adaptation regulation of a tumor-bearing organism as close as possible to practice in an integrated treatment of malignant tumors with the use of the technologies of the activation therapy illustrated by the examples of some electromagnetic field exposures and pharmacological actions (xenon therapy).

Materials and methods

Our research work has used the clinical data on 1310 patients who have been diagnosed with cancer of different localization: breast cancer (n = 170), cervical cancer (n = 60), lung cancer (n = 760), bladder cancer (n = 120), brain gliomas of high grade of malignancy and metastatic damage (n = 170) and extended colorectal cancer (n = 30) and who have completed their treatment at the National Medical Research Centre of Oncology of the Ministry of Health of the Russian Federation (Rostov-on-Don). The total number of the patients, who have received the specialized anti-tumor treatment in combination with an accompanying therapy based on the methods of the designed activation therapy, is 1310 individuals. Our research report gives an analysis of some examples of the applications of the electromagnetic and pharmacological methods of the accompanying therapy in the cancer treatment.

At the stages of the integrated anti-tumor treatment we have employed different types of the accompanying therapy: the technologies of the central (the targeted hypothalamus area), local (the tumor bed resection area), extracorporal (blood) actions with the use of electromagnetic field of the extremely low frequencies (ELF MF), the extremely high frequencies (EHF MF), the optical spectrum frequencies, the pulse-type frequencies of magnetic field (PF MF) and the scanning frequencies of magnetic field (SF MF).). For the purpose of generation of the above types of magnetic fields in different programmable modes of frequencies, induction and exposures, we have applied some microprocessor-controlled magnetotherapy devices of product line GRADIENT 1-4 (manufactured by GRADIENT Ltd., Rostov-on-Don, Russia) and the extendable NEURO-MS/D therapy device produced by NEUROSOFT (Russia). We have utilized new programmable regimes of xenon therapy (XT) involving the therapeutic circuit for xenon inhalation with gas flow control CTC-1 (made by XeMed, Russia), the GCM-03-Insovt combined medical gas analyzer (produced by CEC INSOVT, St. Petersburg, Russia), and medical xenon dosing equipment DCM-001 (produced by AKELA-N Ltd., Russia). All experimental research records have been properly prepared in full conformity with the ethical standards of the Declaration of Helsinki (adopted in 1964, Revision 2013) and duly approved by the Commission on Bioethics at the Federal State Budgetary Institution "National Medical Research Center of Oncology", Rostov-on-Don, the Ministry of Health of the Russian Federation.

Results

Accompanying electromagnetotherapy of lung cancer. Our analysis of the immediate outcomes of the surgery treatment of lung cancer shows that there is a reduction in the total post-surgery complication cases in the patient group (n=126) after the ELF MF central exposure (targeted at the hypothalamus), which is 1,7 times less than in the reference group of the patients (n=270), who have not been exposed thereto (19,9 and 34,3%, respectively). In this case, the post-surgery lethality rate has been recorded to be 2,3 times lower (from 7,3% to 3,2%), and reported has been an increase in the reliably significant 3-year-survival rate in patients with non-small cell lung cancer (NSCLC) grade I as against those patients, who have undergone surgery only: 79,1±5,6 and 64,3±3,8% ($p<0,05$), respectively [13].

The multi-level mechanisms of the accompanying activation therapy are realized at the level of the adrenal cortex (the cortisol concentration has been decreased from 413±31,7 to 336±30,7 nmol/l, and the high level of the stress-related adrenaline has been found to be reduced from 42,1±5,1 to 26,3±7,4 nmol/day), the epiphysis (normalization of the melatonin formation function), the thyroid glands, the androgenic region of the adrenal glands and the gonads, suppressed functionally by surgery-associated stress, as well as the immune system (we can note a pronounced improvement in the immune status in our patients [14, 15]. The physiological correlates of the anti-stressor effect produced by ELF MF are stabilization of the indicator of the spatial synchronization of the cortex bio-potentials of the rhythmic activity of the brain and increasing in power by the α-rhythm (from 1900 to 2180 arb.u.) in combination with a rise of the β-rhythm power by a factor of 2,9 [16].

1. *Accompanying therapy with the use of ELF MF, CMF and PF MF in treatment of high-grade glioblastomas*

The results from the complex treatment of high-grade glioblastomas (HGG) have demonstrated that the use of the programmable double mode of the activation magnetotherapy (ELF MF applied to the projection of the hypothalamus and CMF exposure of the surgery area) in the course of the chemoradiotherapy shows that the sustained remission upon completion of the treatment has been achieved in 25 of 30 patients (93,3±4,6%), who have received chemoradiotherapy in combination with magnetotherapy that is 2,3 times more frequently than it is the case with those patients who have been subjected to the conventional chemoradiotherapy only (12 individuals, 40±9,1%) [17].

The progression of the disease has been observed in the main group in 2 patient cases only (6,7±4,6%), while in the group of the patients receiving the conventional chemoradiotherapy recorded have been 14 disease progression cases (46,7±8,5%), i.e. it has been found 7 times more frequently. It has been reported that all patients in the main group have survived till the end of course 4 of their medication therapy, while another group to be compared have demonstrated 4 lethal cases (13,3±6,1%) recorded within the same time span (see Figure 1 herein).

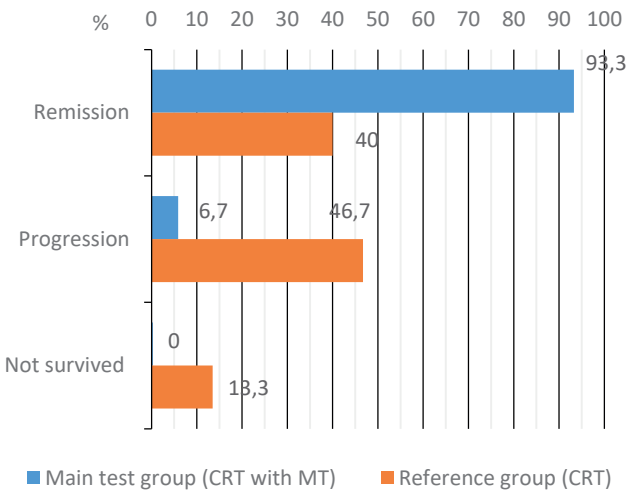

Figure 1. Comparative efficacy of chemoradiotherapy depending on application of accompanying therapy with ELF MF and CMF in patients with brain malignant gliomas

The application of the designed doubled programmable mode (ELF MF and PF MF) of the transcranial magnetotherapy (TMT) as a factor of the accompanying treatment, beginning with post-surgery day 2, has resulted in a decrease in a ratio of the average values of the residual tumor volume (recorded as 2,3±0,7 cm^3 in the main group as against of 6,7±2,4 cm^3 in the reference group; p≤0,05) and a ratio of the average values of perifocal edema (1,43±0,34 cm^3 in the main group as against of 2,7±0,5 cm^3 in the reference group; p≤0,05). Upon completion of the radiotherapy in combination with TMT, observed is a prolonged regress of the post-operative edema to a value 3.8 times less than the initial ones. Neurovisualization of changes in the tumor volumes and the perifocal edema at the pre-operative and the post-treatment stages makes possible to clearly define the efficacy of the TMT application in the HGG patients (see Figure 2 herein).

In case when TMT is included into the scope of the integrated treatment of HGG, there is a significant increase revealed in the total 6-and 12-month survival of the main group patients as against those in the reference group: the values have been reported to be 100% versus 88,8±8,7%, and 68,5±10,4% versus 52,0±7,5%, accordingly (Log-Rank test, p=0,001). The NIHSS scoring in the patients upon completion of the radiotherapy has confirmed that neurological symptoms have been mitigated in 84% of the patients with the applied TMT as against of 48% of the patients who have not received TMT (p≤0,05). TMT has contributed to the restoration of the cognitive functions (measured by the MoCA) that has been observed 3,4 times more frequently than before radiotherapy and 4,0 times more frequently after the completion of the latter as compared with the reference group. A similar posi-

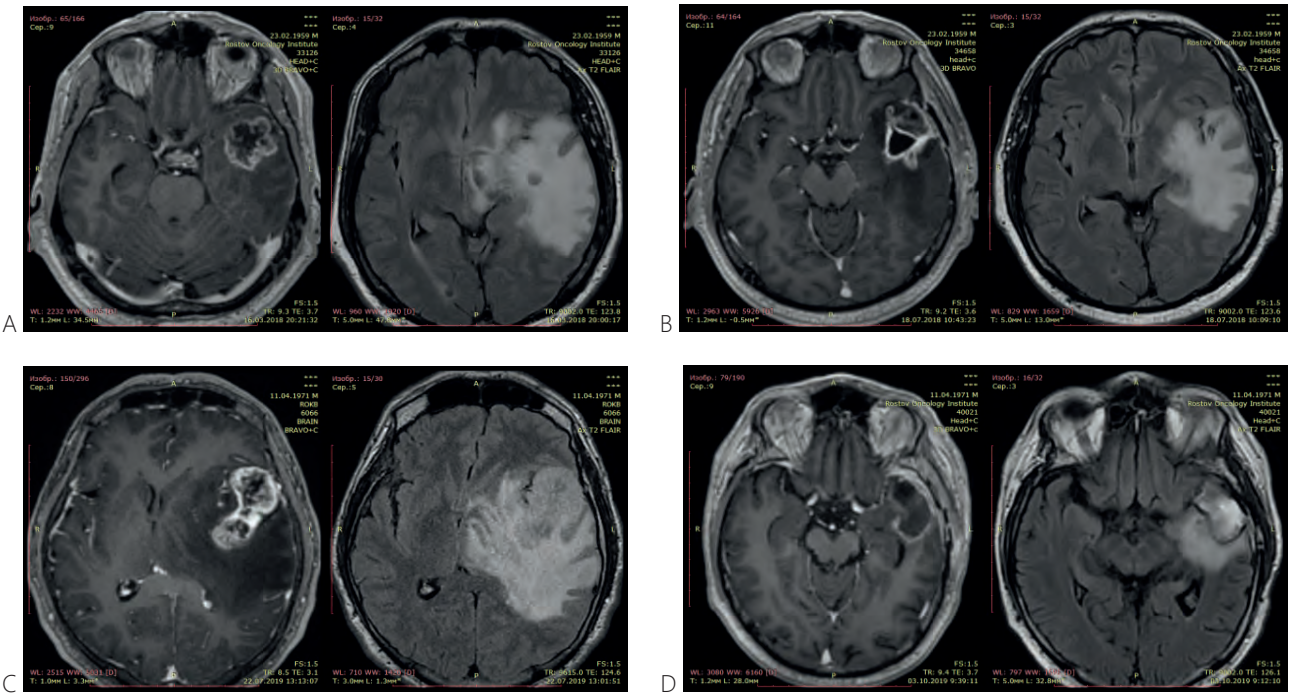

Figure 2. Examples of MRI images of a patient in the reference group: A – before treatment; B – in post-surgery and radiotherapy period. Examples of MRI images of a patient in the main test group: C– before treatment; D – in post-surgery and radiotherapy period with the use of accompanying TMT. Note: There is a tumor (or a post-surgery cavity) in axial projection, with applied enhanced contrast 3D BRAVO, exhibited in the left part in each image; the right part in each image shows a brain substance edema with applied T2 FLAIR.

tive dynamics is noted in measuring the Barthel index (p≤0,05) as well as Karnofsky Performance Status scoring at a level of 90 reaching in the main group 60±7,1%, as against 27,3±9,5% in the reference group (p≤0,05) that has reflected the functional neurological and cognitive preservation and increased quality of life in the HGG patients [18,19].

2. *Method of accompanying therapy under intravesical chemotherapy conditions*

We have developed a method of the targeted delivery of medical drugs due to enhancement of permeability of the bladder tissues in case of intravesical therapy by scanning the frequency of the signal in the projection of the bladder and complexing the spatial structure of the field with the use of the CMF vaginal inductor [20]. In doing so, the local subcutaneous action has played a role of a trigger to induce the required integral adaptational reactions. When conducting our experimental trials to learn more about effects produced by SF MF on penetration of the chemotherapy drugs through the membranes of the tumor cells, we have applied fluorescence microscopy. Using the potential-sensitive probes, we have evaluated the intensity of fluorescence of the medical drugs that reflects their content or concentration in the cells. So, upon delivery of doxorubicin or cisplatin, in combination with the SF MF exposure, it has been reported that the citostatic accumulation in the S-45 cells is double as much as it is the case in the reference assay (see Figure 3 herein) [21].

In this case, SF MF has increased the membrane potential in live tumor cells by 80%. In order to accelerate the diffusion rate of cisplatin, the SF MF action has been enhanced by a magnetic field constant component (CMF). Due to a combination of SF MF and CMF, the gain in efficacy of the exposure has been recorded to be not 2, but 5,9 times (see Figure 4 herein). The developed methodology and technique has been duly patented [22].

When studying impacts produced by SF MF and CMF in combination with gemcitabine on the bladder cancer cell suspension, we have obtained evidence data that an accumulation of the above anti-tumor drug on average is increased. The effect of an increase in the

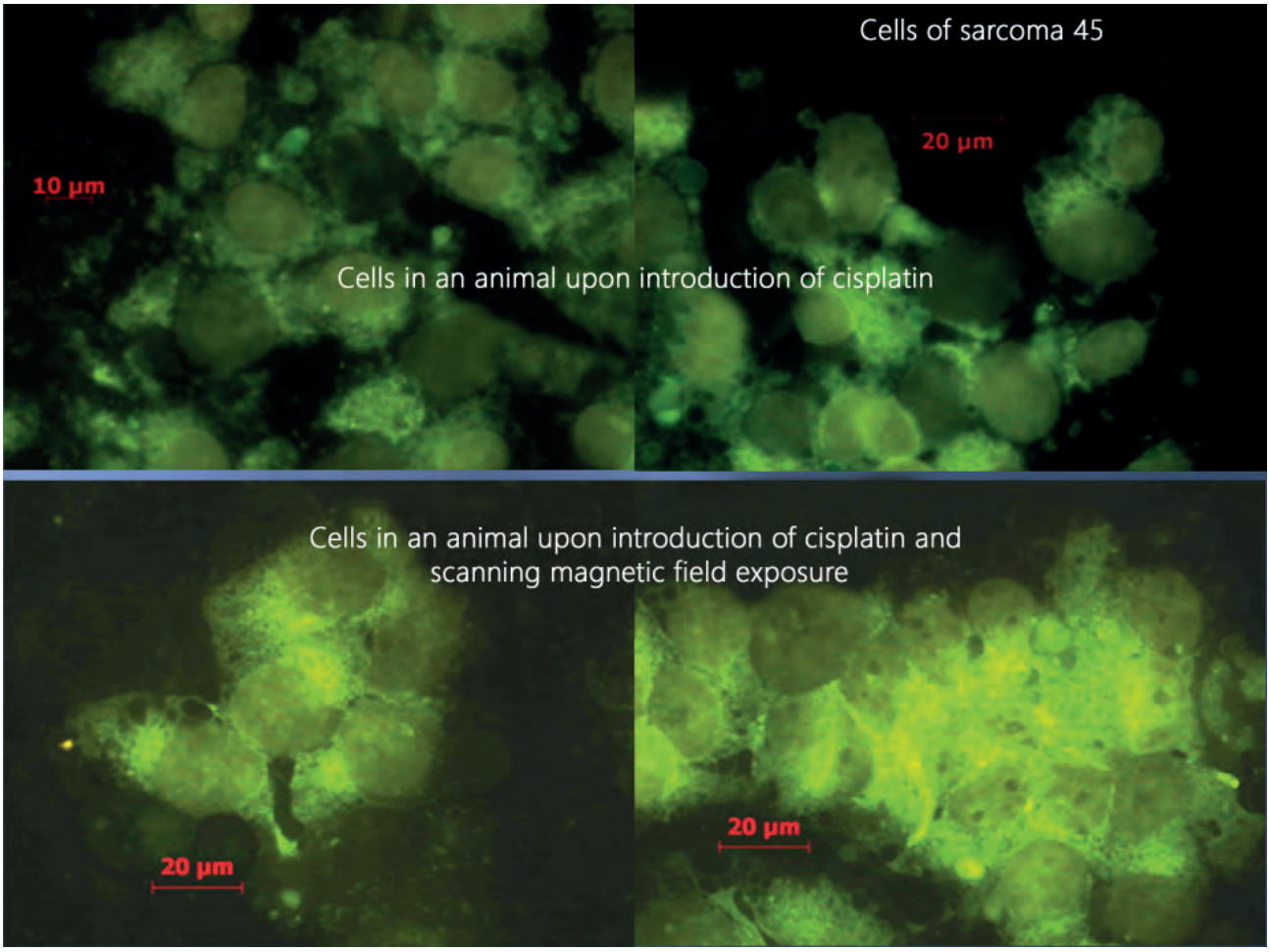

Figure 3. Different intensity of fluorescence of cell sarcoma-45 associates upon effects produced by cisplatin supported by scanning magnetic field exposure and without SF MF therapy.

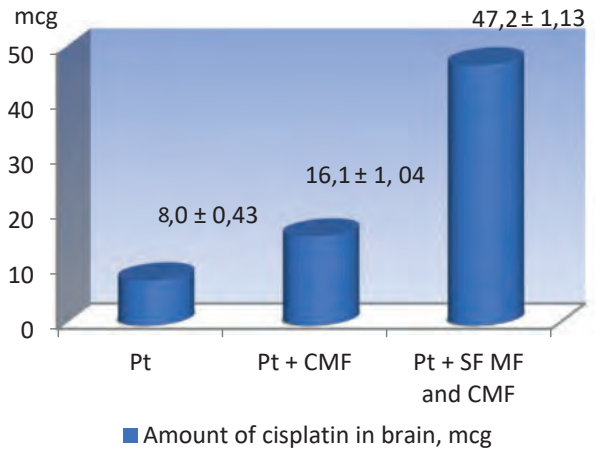

Figure 4. Accumulation of cisplatin in tumor tissue upon SF MF and CMF exposure

membrane penetration for a polar lipophilic molecule under the SF MF exposure has been confirmed by the calculations of a ratio between the intensity of fluorescence without the above mentioned exposure to that with the exposure of the tumor cells In_{ie} / In = 0,42.

The technique of the adjuvant intravesical gemcitabine chemotherapy of non-muscle-invasive bladder cancer patients accompanied by the parallel local treatment with SF MF and CMF exposure have made it possible to statistically reliably improve the 2-year relapse-free survival (RFS) from 77% in the reference group to 94% in the main test group (Long Rank Test=2,089;p=0,036) as well as to double the latent relapse period as a result from the restraining and preventing effects of the accompanying therapy [20]. We have succeeded in a reduction of dysuria as the local effect by a factor of 1,5 and symptoms of weakness and nausea by a factor of 1,6 as compared with the reference group, as well as in a decrease in the C-reactive protein value (1,75±0,15 against 9,58±1,52 before treatment; p<0,0001), in the molecules of the median weight (MCM254: 0,298±0,017 against 0,335±0,029 before treatment, p=0,01; MCM280: to 0,319 ±0,019 against 0,422±0,044 before treatment, p<0,001) [20, 23].

Our investigation of the adaptational reactions in the course of the adjuvant therapy bears witness to the fact that there is a considerable increase in the rate of occurrence of the anti-stressor reaction of calm activation (60,0% against 33,3%; p<0,001) under normalization of the immune regulatory index CD3+CD4+/CD3+CD8 and a rise in the NK-cell content by a factor of 1,9 that indicates that there is a relationship between the cell-level-related and the integral mechanisms of the preventive and anti-relapse effects made by scanning frequency electromagnetic field included into the treatment schedule [20].

3. *Accompanying therapy in locally advanced breast cancer treatment with use of optical magnetic treatment of blood*

In our experimental studies in vitro, it has been found that the visible electromagnetic radiation of red with a wavelength of 0,67 mcm, a dose of 1,5 mcc with a magnetic field induction of 10 mTl at a frequency of 0,3 Hz and an exposure of 3 minutes makes impact activating the key enzymes of the energetics of lymphocytes [24]. In this case, the concentration of the activated cells at the level of succinate dehydrogenase is increased by a factor of 2,1, and that of glycerophosphate dehydrogenase becomes 1,3 times higher. It has been revealed that the experimental chemotherapy modified by the visible electromagnetic radiation reliably results in the lowering of the C-45 growth index by 20±1,8%, the regression rate by 25,±1,5% and prolonging the life span by 27±2,1% (P<0,05) in animals.

The neo-adjuvant auto-hemochemotherapy modified by the visible electromagnetic radiation in the integrated treatment of locally advanced breast cancer patients has made it possible to improve the immediate outcomes of the treatment due to elevation of the general regression effect as against the standard polychemotherapy by 20% (P<0,05), accordingly, due to a reduction in the process progression cases by a factor of 3,5 and 1,5, respectively, due to a diminishing of general toxic reactions, including leikopenia grade II and II, providing a three-year general and event-free survival in 93% and 97% of the patients that is 30% higher than it is the case under the system- and auto-hemochemotherapy (P<0,001).

When studying the treatment pathomorphosis in breast cancer tumors under the medical drug therapy modified by the visible electromagnetic radiation, noted have been an increase in the number of cells changed dystrophically (227±11,2 against 189±8,4 and 109,7±9,4‰ in the comparison group and in the reference group, P<0,05), a reduction in the the parenchyma area (17,1±0,9 against 20,4±1,1 and 30,5±1,2%, respectively, P<0,05) and an increase in the stroma area of the tumor (82,3±4,5 against 75,6±4,2 and 66,9±3,2%, P<0,05) (see Figure 4 herein).

The tumor cell populations upon the effects produced by the modified AHCT have demonstrated their difference not only in an increased amount of the damaged tumor cells, but also in a pronounced lym-

phoplasmacytic infiltration (LPI) that has not been reported for the reference group. Considering the fact that the immune competent activated cells being the major population kind, responsible for killing the cells with alien antigenic properties, have shown an effect of their concentration in the stroma and parenchyma of the tumor, it may be suggested that it is just the reason why it has favored developing of necrosis and resorption of the tumor cells.

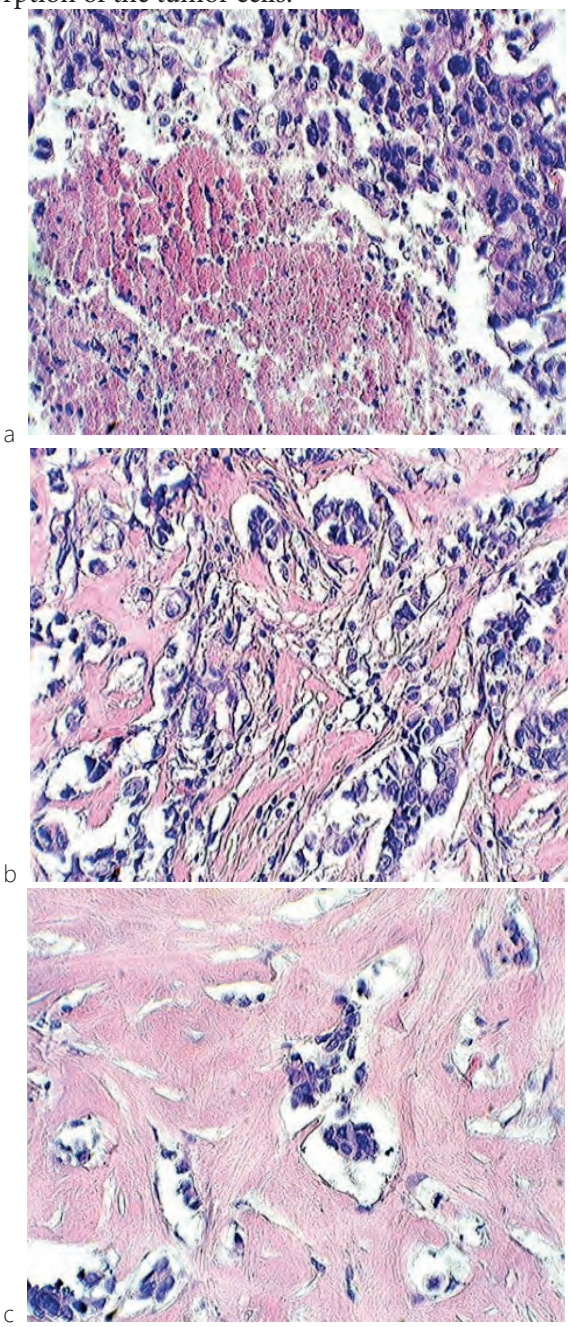

Figure 6. Morphological alterations in the tumor: a) the reference group: an extensive necrosis against the background of the remaining, but dystrophically altered tumor cells; b) the reference group: accumulations of dystrophically altered tumor cells against the background of stromal hyalinosis; c) the main test group: stromal hyalinosis and small complexes of dystrophically altered tumor cells. Magnified x400.

An important component of the anti-tumor effect of the auto-hemochemotherapy modified by the visible electromagnetic radiation has been a change in the hormones secreted by the hypophysis: the initially recorded increase in the prolactin secretion has been normalized in 43% of the cases; the normalization of the follicle-stimulating hormone (FSH) level has been found in all breast cancer patients, completed the therapy, as compared both with the respective initially elevated and lowered levels, that bears witness to the fact that the central mechanisms of the regulation of homeostasis in a human organism has been activated [24, 25]. It has been evidenced by a pronounced predominance of the anti-stressor reactions over stress and by an increase in their ratio by a factor of 1,4-1,8 at all stages of the neo-adjuvant therapy accompanied by the visible electromagnetic radiation therapy [24].

4. *Restorative xenon therapy of fertile oncological women after cervical cancer surgery (CC) and breast cancer surgery (BC)*

An issue of particular concern is the current tendency of increasing the occurrence in young females diagnosed with CC and BC [26]. As a result, in fertile women after the hormone-reducing surgical treatment, conditions are produced, which initiate some pathological syndromes as given below: the post-mastectomy syndrome after radical breast cancer surgery, post-castration syndrome developed after total ovariectomy in oncological gyneacology or their simultaneous variant due to surgical castration in case of hormone-positive BC and concurrent genital pathology. The loss of fertility involves a limitation in active participation of the significant contingent of labor resources of this sort, who have already reached the required occupational qualification, competence and status, in the social life, considering both family and economics. Searching for ways to properly solve this critical issue remains an object of attention to leading oncologists both in Russia and abroad [27-29]. In order to increase the efficacy of the rehabilitation therapy, required is a selection of factors, which are capable of demonstrating their preferential poly-systemic protective action [30, 31].

We have developed an algorithm of exponential programming of low-dosage xenon therapy of the post-castration syndrome in fertile cervical cancer patients that has been confirmed by a significant decrease in the menopausal index value (scoring under moderate grade from 47,4±3,0 to 36,3±1,1 (p=0,002),

and scoring for severe grade from 66,1±2,1 to 57,5±1,5 (p=0,001)); in breast cancer patients with surgical castration (scoring under moderate grade from 48,8±1,4 to 37,2±1,3 (p=0,002), scoring under severe grade from 68,1±2,1 to 54,0±1,2, respectively, (p=0,003)), mitigation of post-operative pain in 96,8% of the cases, a reduction of pathological symptoms by a factor of 2-6 in testing quality of life according to the ESAS and MOS-SF-36 criteria [32, 33]. The xenon therapy has favored eliminating the estrogen-deficit state with an elevated level of estradiol to 751,4±61,4 nmol/l as against 436,2±21,1 (p=0,001) in the reference group. The post-castration syndrome in the BC group with surgical castration, where the xenon therapy has been used, has been followed by the normalization of the humoral normalization evidenced by the absence of elevated levels of prolactin, estradiol, LH and cortisol in blood that has been recorded in the regular therapy patients without xenon treatment technique [34]. The completion of the course of the programmable xenon therapy of the post-castration syndrome in the fertile CC and BC patients has initiated a restoration of the rhythmogenesis by the brain, an increase in the blood anti-oxidant activity, a recovery of glutathione system, a stable maintenance of the integral nonspecific anti-stressor reactions as the mechanisms responsible for correction of the adaptation processes and an improvement in quality of life in the early post-surgery period [34, 35].

4. *Accompanying xenon therapy aimed at optimization of radiotherapy in patients with brain metastatic lesion*

One of the options to improve the local control is to give an extra local radiation dosage: a radiation boost that allows achieving an escalation of the dosage within the area of the pathological focus and, as a result, raising the effectiveness of the conducted therapy in general. An extended randomized study known as RTOG 9508 has demonstrated that a combination of the total and local radiation exposures makes possible both to obtain a sound level of the local control and provide prolongation of the total life span in patients with some isolated metastases, however it is still disputable how to properly specify the required dosage and time of the local radiation exposure [36]. In order to provide a better tolerability of radiotherapy and an enhancement of its anti-tumor effect, it seems to be reasonable to give jointly the boost radiation and the radiotherapy covering the entire brain as a whole accompanied by xenon therapy.

The development and application of the original technology of the radiation therapy of metastatic disease of the brain, based on the combination of the total (the brain-targeted) and local (targeted at the removed metastatic focus) radiation delivery has allowed reducing the rate of episodes of continuing tumor growth from 15% to 15% (p<0,05). It should be mentioned that the obtained effect has become more pronounced (a decline in the above incidence to 10%) due to incorporating another accompanying therapy factor, namely, xenon in the form of the xenon-oxygen inhalation, in the double-radiation exposure schedule. The clinical significance of the accompanying xenon therapy has been evidenced by the data showing an increase in the 2-year survival from 17% to 22% in the cohort of the brain metastatic disease patients that has resulted not only in the prolongation of their life span, but also in improvement in quality of their life. [37].

The utilization of the accompanying xenon therapy at the stages of radiation therapy according to the designed methodology has contributed to an improvement in quality of life in the patient category with a significantly less pronounced neurological symptoms: as to motor functions, by 4,2 times (scoring from 26,7 to 6,4), considering coordination, the decrease is reported to be by 6 times (scoring from 20,0 to 3,3) and the headache pain intensity by 2,6 times (scoring from 43,3 to 16,7). In this case, we have recorded a reduction in the number of disorders according to criteria "memory" from 26,7 до 16,7, "attention concentration" from 36,7 to 16,7 and "general feeling" from 20,0 to 3,3 (p<0,05) that has not been observed under applications of other treatment options.

The evidence for the anti-stressor and anti-catabolic effect of the proposed method is a significant decrease in the level of cortisol in serum recorded by the end of the treatment in patients with isolated metastasis in the brain: in males by a factor of 8,5 (from 542,1 to 64,0 nmol/l), and in females by a factor of 15,5 (from 559,3 to 36,2 nmol/l). In males, who have received the xenon therapy, reported is also a decrease in the level of prolactin by 2,6 times (from 265,1 to 100,9 μIU/l) and an increase in the level of estradiol by 1,8 times (from 271,9 to 478,9 pmol/l). Besides, revealed has been a rise in stress resistance coefficient DHEA-S/cortisol in males from 0,47 to 0,94 (p<0,05) and in females from 0,31 to 1,16 (p<0,05). We have

recorded the normalization of the rhythmic activity by the brain cortex. In this case, the coefficient showing a ratio between the integral reactions anti-stress/stress in a human organism has been increased by a factor of 3,2 that reflects the realization of the mechanism of the multi-level regulation of the homeostasis and elevation of the nonspecific anti-tumor resistance by the human organism [37, 38].

So we can finalize the evidence data obtained in our research work and ensure that it is expedient to apply the targeted accompanying therapy at the stages of complex treatment of malignant tumors with different localization. In doing so, it is essential that the electromagnetic or medical drug actions and exposures, regardless of the nature of the applied factors, employed under the developed programmable modes, shall address the triggering mechanisms of the nonspecific adaptational reactions of the anti-stressor type. It serves as a groundwork for the realization of the activation processes at all hierarchical levels in a human organism and contributes to the restorative dynamics of the regulatory systems (the nervous, endocrine, immune systems and the anti-oxidant protection system).

By this means the theoretical substantiation of the approaches to accompanying therapy in the context of conceptual philosophy of the system of the general adaptational reactions, differing in their nature, the criteria of their development, the principles of their applications and development of new technologies, based thereon, enable us to arrive at a solution of the problem how to provide an adequate control of the resistance of a tumor-bearing organism, how to considerably increase the efficacy of the anti-tumor treatment, how to prolong the life span in this sort of patients and raise their quality of life.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Structural oncomarkers in blood plasma in patients with multiple myeloma when using accompanying selective plasma exchange and chemotherapy

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Abstract

The aim of this research work has been to investigate the structural organization of solid films made from blood plasma taken from patients with secretory multiple myeloma (MM) and identify some specific markers of the tumor process in them, when conducting selective plasma exchange and medication.

Using **the methods** of wedge- and edge-shaped dehydratation, we have completed morphological screening of solid samples of blood plasma in 25 patients primarily diagnosed with multiple myeloma (MM).

The obtained results are characterized by profound disorders in the processes of self-organization with predominance of some pathological morphotypes of facias having systemic and local signs of intoxication and paraproteinemia, which correlate with their equivalents revealed in the respective biochemical tests. It has been found that development of multiple myeloma is accompanied by formation of some oncomarkers specific to this sort of oncopathology. The identification of the oncomarkers have been confirmed by the formation of the pathological aggregation of anisotropic micro- and macrospherolytes, which have demonstrated degenerative transformations upon completion of chemotherapy: they have been shaded because of producing complex compounds with chemotherapy drugs or metabolites of the latter.

Conclusion. By this means the cascade of the pathological events have been reflected in our screening morphological assays of blood plasma that is of great prognostic value and may be used in evaluation of efficacy of treatment of multiple myeloma.

Keywords

Multiple myeloma, Morphology of blood plasma, Oncomarkers

Imprint

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Introduction

It is well known that the appearance and progression of many malignant tumors result in certain pathological alterations of metabolic processes and escalation of disorders in homeostasis in the organism of oncological patients [1, 2]. In particular the progression of multiple myeloma (MM) is accompanied by hyperproduction of monoclonal immunoglobulins that involves the appearance of the organ- and system-related disorders, formation of the syndrome of endogenous intoxication against the background of renal lesions [3, 4]. The rationale for an application of the pathogenetic approach to the management of the specific anti-tumor treatment requiring an introduction of selective plasma exchange as the functionally significant component of detoxication is absolutely evident since that is addressed the mechanisms of realization of an effective treatment and an improvement in the homeostasis indices [5, 6, 7]. When conducting extracorporal detoxication, nowadays super-permeable membranes with a high diffusion clearance have been widely used, which make possible to remove the entire spectrum of the middle- and high-molecular toxic substances up to 75000 kDa up to and including albumin molecules. It enables us to reason that the above technique application may be effectively used in patients diagnosed with MM, however required are further clinical and laboratory evidence data.

The completed screening of assays of the proper detoxication substrate with the use of advanced techniques of visualization of solid samples of biological liquid [8, 9] has revealed that the implicit hidden objective information is converted into explicit visu-

al data available at the supramolecular level that expands the possibilities and capabilities of diagnostics of patients primarily diagnosed with secretary MM. It should be considered that the molecular-genetic, immune-histological, biochemical, instrumental and biomedical engineering techniques play the prime role in the diagnostics of tumors, while very often ignored is a unique possibility to trace the behavior of complex dynamic fluids in a human organism, which actually are immediate participants and carriers of integrative data in a human organism. In fact, biological fluids (blood serum and plasma, liquor, urine, ascites fluid), upon their dehydratation, due to conformational transitions of molecules of protein and lipids are portrayls capable of disclosing unique data on the processes of self-organization at the submolecular level in order to gain an understanding of the extent and grade of the pathological disorders and assess the treatment efficacy [10-13]. Along with the structural paraspecific markers at the system-related and local level, some specific oncomarkers, namely, the macro- and microspherolytes, produced in an assay sample under the edge-type dehydrataion conditions, are recognized as the most precise diagnostic criteria for assessing the extent or grade of progression of a malignant process. An evaluation of the state and interactions of the macro- and microspherolytes is decisive for the proper identification of the malignant process in question [14, 15]. So, some specific combinations of anisomorphones have been detected in serum in oncological patients with their confirmed diagnosis that has been properly evidenced by randomized double-blind studies carried out by S.N.Shatokhina and V.N.Shabalin [9, 10]. We have succeeded in establishing the specific tropicity of small- and large-sized anisomorphones with a different grade of the double refraction and transformation of this relationship as the tumor process develops, irrespective of the tumor localization, and as anti-tumor chemo- and radiotherapy is applied.

The aim of this research work has been to investigate the structural organization of solid films made from blood plasma in patients with secretory multiple myeloma (MM) and identify some specific markers of the tumor process, when conducting selective plasma exchange and medication.

Materials and methods. The basis for our research work is formed by morphological data on blood investigations performed in 25 patients primarily diagnosed with secretory multiple myeloma (17 males and 8 females), aged from 45 to 70 (62,7±2,2). Before the anti-tumor medication (in total there have been 6 courses of the standard chemotherapy according to the VCD regimen completed), all patients have been subjected to selective plasma filtration [16] with the use of the Ecvalio™ technology of plasma separation.

With the wedge- and edge-shaped dehydratation methods, we have conducted morphological screening of solid samples of blood plasma in the above cohort of the patients. To prepare solid-state blood serum samples, venous blood was collected with a sample volume of 2 cm^3; cell elements were separated by centrifugation, and the obtained bio-fluid was applied as 3 droplets onto a glass slide with a volume of 10 μl. The time of the dehydratation process according to the wedge-type dehydratation technique was 18–22 hours; this procedure was carried out at a temperature of 22–24° C with a humidity of 65–70% in open air avoiding direct air flows. The method of the edge-type dehydratation implies the application of the same ambient parameters, but in doing so, one blood plasma droplet is covered with a cover glass und left for 72 hours to complete the dehydratation, which takes place on the edge of the assay sample unit. The conditions have provided complementary pulling together of oncogenic proteins into zones of the local concentration and formation of the morphones as the specific structural oncomarkers. The morphostructure of the solid-state film of serum has been assessed using light, dark and polarization microscopy with the Leica DMLS2 microscope magnified from x40 to x100. The major criteria for an assessment of the processes of self-organization upon wedge-type dehydratation are identifying the morphotype of a facia (radial, partially radial, irradial, circular, double facia) and revealing the local paraspecific markers of a malignant process (intoxication, paraproteinemia). This method has made it possible to properly estimate various systemic disorders, among them some abnormalities in the cardiovascular system performance upon a multicourse chemotherapy regimen in breast cancer, in case of brain tumors, soft tissue sarcoma, malignant tumors of the brain, ovarian cancer, oral cancer and cancer types of other localizations [9-12]. The edge-type dehydratation has been employed to identify the presence of the specific oncomarkers and their structure.

The results of our research have demonstrated that the debut of secretory multiple myeloma is featured by progressing endogenous intoxication determined

first and foremost by the pathogenetic mechanisms responsible for the malignant process formation. So, we have revealed that there are high concentration levels of paraprotein, kappa and lambda free light chains (FLCs). The prevalence of the κ-FLC secretion more than 3 times might be attributed to the fact that the number of the plasmatic cells responsible for their production is doubled. β_2-microglobulin is one of the significant markers of the activity of the process under lymphoid tumors. The degree, to which the concentration of the latter in blood is increased, is directly related to the tumor mass and the process intensity. The blood concentration of the β_2-microglobulin recorded at the initial examination in the patients has been found to be more than 4 times higher than the respective physiological norm. In this case, the level of the β_2-microglobulin in patients with cancer stage III has been detected to be twice as much as the concentration thereof recorded in the cancer stage II patients. Greater values have been reported for those patients who have shown clinical signs of renal insufficiency as compared with those without renal function disorders. Before the treatment, against the background of intensive production of pathological albumins, we have observed a decrease in the total and effective albumin concentration by a factor of 1,3 and in its binding capacity on average by a factor of 2 as against the respective indicators in healthy individuals. When investigating the processes of self-organization upon completion of the wedge-type dehydratation of blood plasma, prior to start of the selective plasma exchange (SPE) procedure, it has been found that the morphological pattern before SPE has been characterized by the dominance of the pathological morphotypes of facias: they are irradial, circular (see Figure 1 a herein), "double" facia; at the same time there have been detected a great deal of markers of the pathological processes: endogenous intoxication, paraproteinemia, which has been identified by richly available vermicular structures (see Figure 1 c,d herein). Upon completion of detoxication, in the solid films of blood plasma we have revealed formation of the normal types of fa-

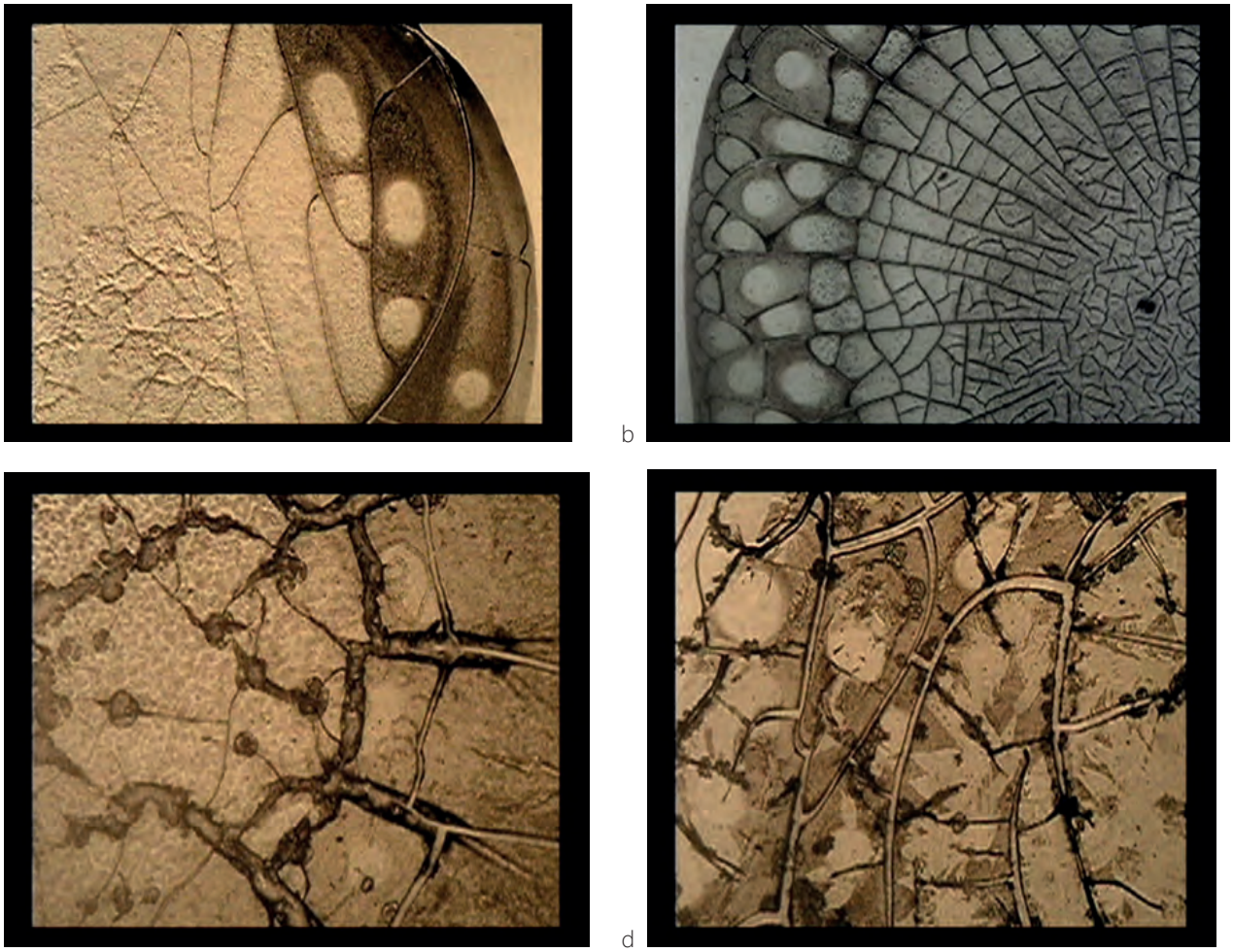


Figure 1. Fragments of facias of blood plasma: a – before treatment, an example for a pathological structure of circular type; b – formation of radial type of facia upon completion of selective plasma exchange; c,d – vermicular structures at an increase in the level of paraprotein over 15%.

cias and a significant reduction in the occurrence of the paraspecific markers.

When analyzing the results obtained in studies on the edge-type dehydratation samples, it has been established that the normal types of anisomorphones, having primarily a large, regular rounded shape, representing basis spherolytes, are rarely found within the assay sample (see Figure 2a herein). In this case, the presence of some loose anisomorphones forming the skeletal spherolytes, which are assumed to be the markers of the immune inflammatory processes, is more pronounced (see Figure 2b herein). Even a low-power magnification enables us to see some destructive changes of the anisotropic macrospherolytes both along the periphery and in the center.

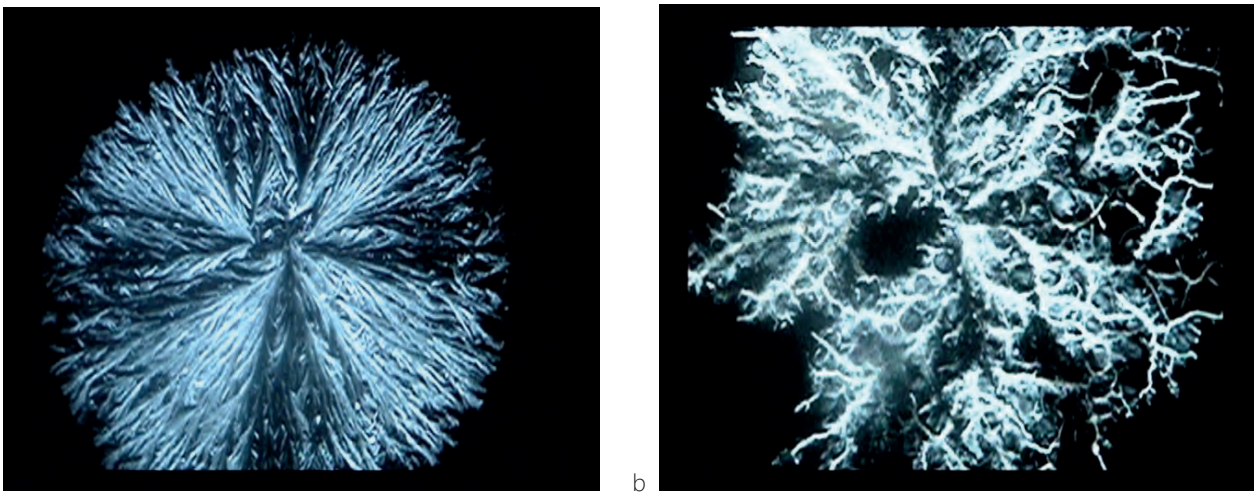
In progression of multiple myeloma, observed have been a pronounced transformation of anisomorphones typical for oncopathology and the appearance of combined forms of the anisotropic spherolytes. The critical condition for the identification of a oncomarker has been the realization of a special process of the aggregation of the micro- and macrospherolytes having the double refraction property. This process has been traced from the time of attaching of the microspherolyte to the edges of the macrospherolyte (see Figure 3a), through the time of its radial advance to the center, finally to the time of its locking there (see Figure 3b-d herein). The formation of the hybrid anisomorphones in blood plasma in patients with multiple myeloma furnishes a unique example of visualization of molecular interactions of protein products of a tumor under crystallization in the assay sample that is closely linked with the progression of the malignancy growth.

The above example shows not only clear-cut stages of the progression, up to and including the appearance of the structural markers of metastasizing, but also reveals the morphological fingerprints of the specific anti-tumor treatment: chemo- or radiotherapy. In the course of the polarization microscopy of plasma in the assay sample (see Figure 3 a-d) we have discovered that upon completion of the selective plasma exchange procedure and chemotherapy some disaggregations of the anisomorphones with destructively changed macrospherolytes with different color tints and shades have been found.

It should be noted that during the chemotherapy even some isolated basis anisomorphones, which have not formed the pathological aggregations at that stage of the medication, have demonstrated a color palette typical for formation of complexes with chemotherapy drugs or their decomposition products (see Figure 4 herein). That has been used as a morphological assessment of efficacy of the anti-tumor chemotherapy with the previously conducted selective plasma exchange procedure.

Based on the evidence data obtained previously by S.N.Shatokhina and V.N.Shabalina [5, 8] that a characteristic for suppression of the tumor growth is a disruption of the aggregation of anisotropic micro- and macrosherolytes, formation of degeneratically altered macrosherolytes followed by their decomposition, we have conducted a visual analysis of the processes of crystallization of plasma in patients with multiple melanoma after their completed chemotherapy.

After the medication, noted have been a disintegration of the structural oncomarker and settling out of the microspherolyte into the surrounding space (see Figure 5 herein). This sequence of the events has been



a b

Figure 2. Fragments of an assay sample of blood plasma in patients with multiple myeloma: a) – preserved basis spherolytes; b) skeletal spherolytes as markers of immune inflammatory processes.

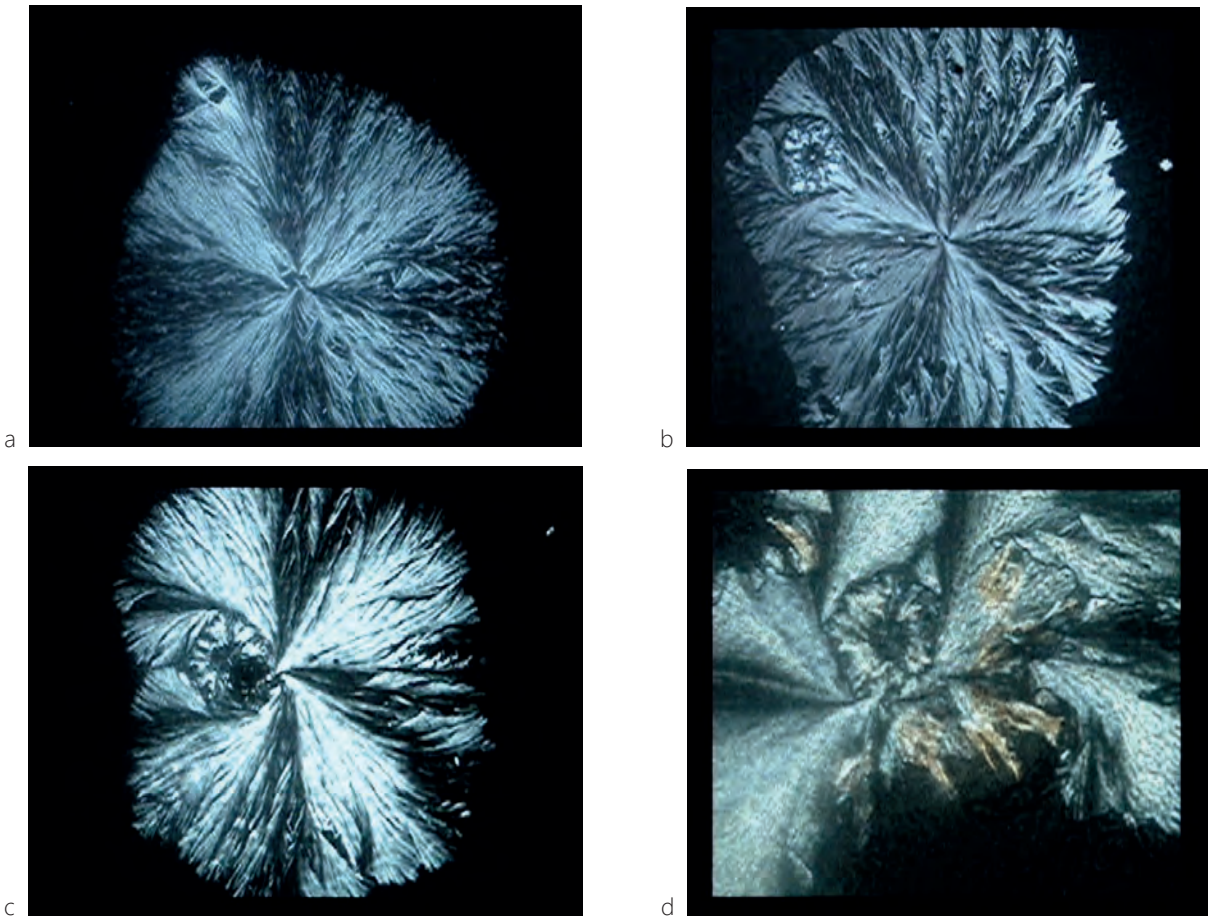


Figure 3. Fragments of an assay sample of blood plasma in patients with multiple myeloma: a – the onset of pathological aggregation of a micro- and macrospherolyte; b, c, d – advance of the microspherolyte to the center of the macrospherolyte and its locking thereto.

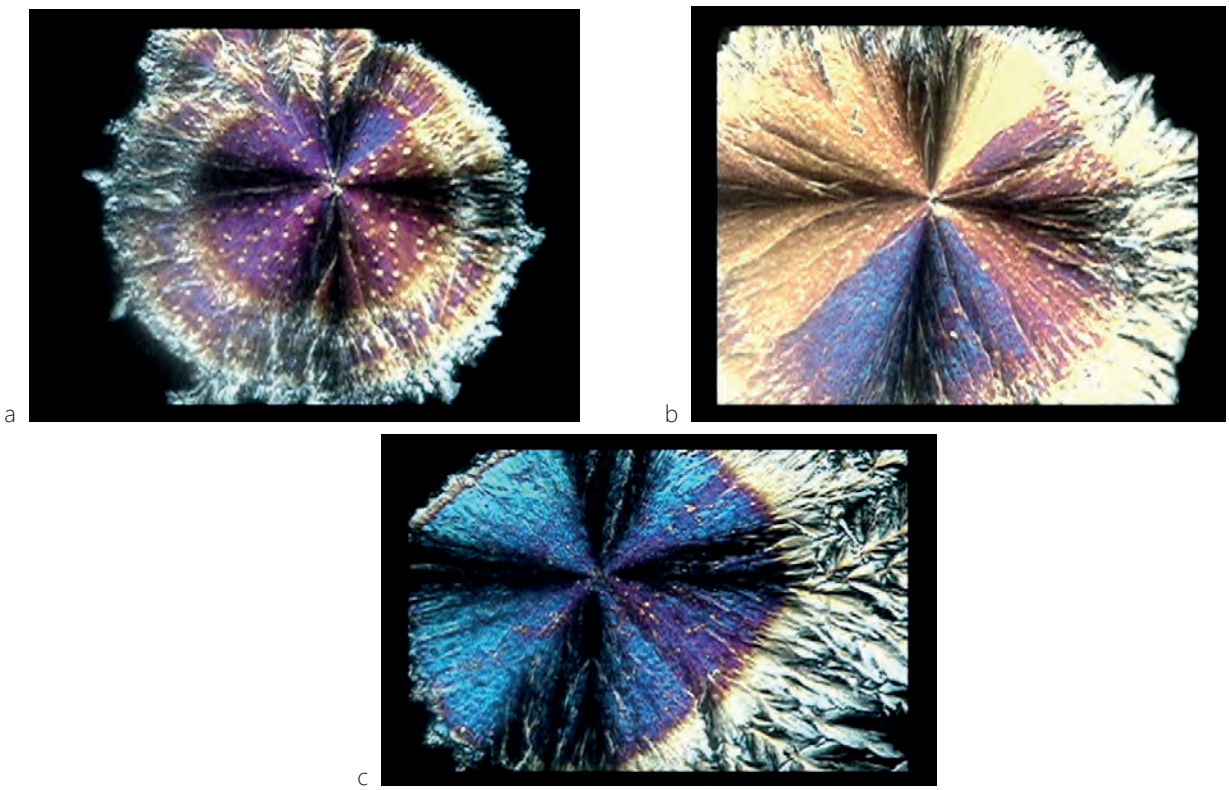


Figure 4. Fragments of an assay sample of blood plasma in patients with multiple myeloma after completion of chemotherapy with the previously conducted selective plasma exchange procedure: a-b – basis anisomorphones (macrospherolytes) with tints of supramolecular complexes with chemotherapy agents.

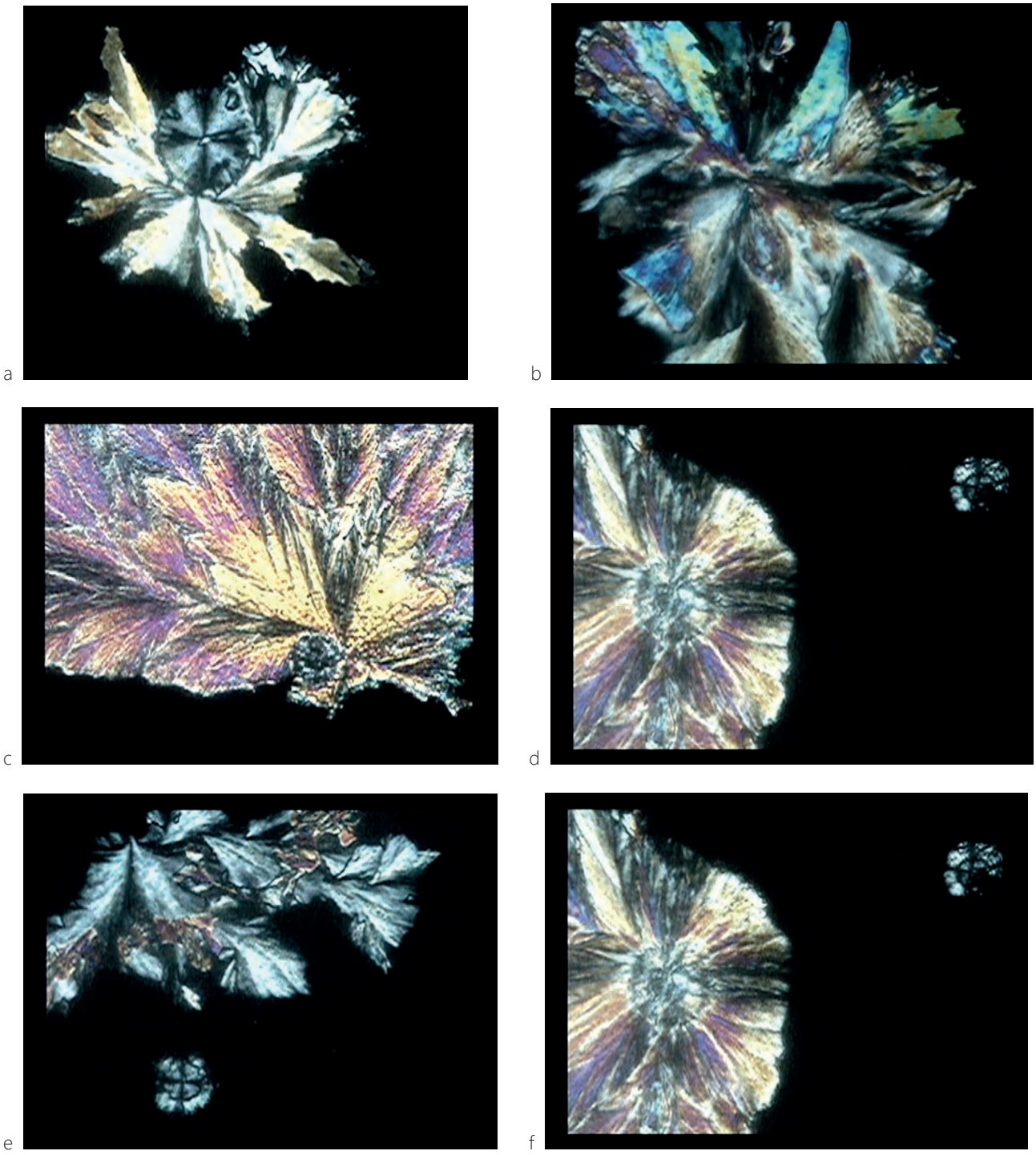


Figure 5. Fragments of an assay sample of blood plasma in patients with multiple myeloma: a-c – disintegration of the structural oncomarker: disaggregation of the micro- and macrospherolyte after completed selective plasma exchange and chemotherapy; d-f – detaching of the anisotropic microspherolyte from the center of the degeneratically altered macrospherolyte after chemotherapy.

confirmed first by the detected destructive changes of the macrospherolyte, acquiring various fan-, needle-type and skeletal shapes, and second by the typical color tints taken by the anisomorphones after the introduction of the anti-tumor drugs.

By this means we can state that the conducted morphological investigation of the process of crystallization in a closed assay sample taken from the MM patients has demonstrated that progression of multiple myeloma is accompanied by the formation of the structural markers specific to oncopathology. The identification of the oncomarkers has been evidenced by the formation of the pathological aggregation of the anisotropic micro- and macrospherolytes, which has been found to be altered after the completed chemotherapy due to the appearance of complex compounds

with chemotherapy agents or their metabolites, with taking some specific color tints. As a consequence of these destructive processes at the supra-molecular level the disaggregation and disintegration of the oncomarkers take place, against which the formation of the normal types of the anisomorphones with the visible properties of the interaction with medication agents has been observed. That bears witness to the prognostic value of the structural markers of blood plasma for the purpose of assessment of efficacy of treatment of the multiple myeloma patients.

By generalizing the results obtained in our morphological studies on blood plasma in the MM patients, we can highlight some key regular patterns. First the assessment criteria of the system-related level of self-organization indicate that there is a profound deviation from the radial symmetry up to the full loss thereof in the formation of cracks under the wedge-type dehydratation of blood plasma. The predominance of the pathological morphotypes of facias like the irradial, circular type or the double facia bears witness to the appearance of pronounced metabolic alterations in the organs of the different systems in the organism under examination. Second an imbalance in homeostatsis has been confirmed not only by the chaotic character of structuring the main elements of the facia (some cracks, irregular discontinuities, concretion), but also by richly available local morphological markers of the pathological processes. We have succeeded in revealing the essential morphological information, which is fully in conformity with the data of biochemistry testing of the level of intoxication according to the data on concentrations of globulines, albumins and particularly paraproteins [17]. In this case, the identifiable network-type vermicular structures and rounded amorphical inclusions of various optical densities have become the morphological correlates of paraproteins. Upon completion of the selective plasma exchange procedure followed by chemotherapy, the observed decrease of the paraprotein level to 50%, downscaling of the middle-weight molecules and the Ig free light chains have resulted in a reduction or the disappearance of these paraspecific markers of the malignancy growth. So, the cascade of the pathological events has been reflected in the screening morphological investigations of blood plasma that has an important prognostic value and that can be used for an assessment of efficacy of the multiple myeloma treatment. Third due to specificity of the crystallization of onco-proteins of blood plasma in a closed assay sample we have confirmed the regularity found previously, which implies high tropicity of small and large anisomorphones with formation of the specific aggregation of the micro- and macrospherolytes as the highly specific markers of a tumor process. The detected signs of the degeneration of the structure of the macrosherolytes with taking by them imperfect, irregular, shapes of the fan-, needle-, skeletal-type, with some other forms among them, taking by them different color tints as a manifestation of forming complex compounds with the chemotherapy agents, have confirmed the efficacy of the treatment of multiple myeloma, including the selective plasma exchange technique. However micro- and macrospherolyte disintegrating and disaggregating has been recognized as the key marker of inhibition of a malignant process.

By this means the application of the technology implying crystallization of blood plasma taken from patients with multiple myeloma on the basis of the wedge- and edge-type dehydratation, that is the best illustrated image of the fundamental processes of self-organization of the bio-fluid, makes possible to visualize the integral changes in homeostasis, the local specific and paraspecific markers of a tumor process in order to predict the disease progression and evaluate efficacy of the anti-tumor therapy used.

Conclusion. It has been found that the processes of crystallization of blood plasma taken from patients with multiple myeloma are characterized by profound disorders and abnormalities in the self-organization processes with predominance of the pathological morphotypes of the facias with the systemic and local signs of intoxication and paraproteinemia that correlates with the respective equivalent data obtained in biochemistry testing. So, we have succeeded in discovering some specific markers of the tumor growth, which represent a pathological supramolecular aggregation of the anisotropic micro- and macrospherolytes and which have the diagnostic and prognostic value indicating possible progression of a malignant disease and efficacy of treatment thereof.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Applicability of mitochondrial energy factors in accompanying therapy of lymphoproliferative diseases (experimental study)

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Abstract

Aim. The purpose of the study was to reveal the effectiveness of the Cytochrome C drug in the early stages of the Pliss lymphosarcoma growth in white outbred rats.

Material and methods. The studies were included white outbred male rats with an initial weight of 180–220 g (n = 40) with subcutaneously inoculated Pliss lymphosarcoma. Rats in the main group received the Cytochrome C intraperitoneally in a single dose of 1.6 mg/kg 1 hour after the tumor inoculation and then until death; animals with tumors in the control group received saline instead of the studied drug in the same way and in the same dosage.

Results. Subcutaneous tumors appeared in the control group in 100% cases, in the main group in 55% cases; tumors were not detected in 45% of animals in the main group. In rats of the main group receiving experimental treatment, tumors regressed with time: in 73% cases with complete recovery of rats, in 27% cases animals died.

Conclusions. The Cytochrome C in a therapeutic and prophylactic regimen had a pronounced antitumor effect. Perhaps the effectiveness of the drug can be improved using an inert carrier which will protect the protein from proteolytic cleavage when it enters the bloodstream, together with detoxification agents.

Keywords

Pliss lymphosarcoma, Cytochrome C, Rats, Tumors, Survival

Imprint

Elena M. Frantsiyants, Irina V. Kaplieva, Valerija A. Bandovkina*, Lidia K. Trepitaki, Ekaterina I. Surikova, Irina V. Neskubina, Julija A. Pogorelova, Natalia D. Cheryarina, Alla I. Shikhlyarova, Tat'jana I. Moiseenko, Maxim N. Duritskii, Sergey V. Tumanian, Yuriy V. Przhedetskiy, Viktoria V. Pozdnyakova. Applicability of mitochondrial energy factors in accompanying therapy of lymphoproliferative diseases (experimental study). Cardiometry; Issue 20; November 2021; p. 29-33; DOI: 10.18137/cardiometry.2021.20.2933; Available from: http://www.cardiometry.net/issues/no20-november-2021/applicability-of-mitochondrial

Introduction

Cancer is a process of "microevolution", when the most adapted cell gains an advantage in survival among a heterogeneous cell population. Therefore, it is logical to assume that carcinomatous cells, which modulate their repertoire of defense mechanisms, are endowed with an advantage of constant proliferation and survival. Two features thereof imply the altered cell respiration and avoidance by the mechanisms of cell death to escape apoptosis, as a result of which cancer cells increase the mass of tissue and become resistant to clinical treatment regimens [1]. Mitochondria, which are the center of energy functions, are the key to the life and death of a cell [2]. Cell survival depends on various critical functions of the mitochondrial membrane, which shows significant morphological changes at the initial stages of apoptosis [3]. Cytochrome C is an evolutionarily highly conserved protein localized in the mitochondrial intermembrane space, and it is the last oxygen-receiving enzyme in the respiratory chains, and it is considered to be the final stage of the mitochondrial respiration. Internal apoptosis is closely linked with the permeability of the external mitochondrial membrane and the subsequent release of the cytochrome C protein into the cytosol, where it can participate in the activation of caspases through the formation of apoptosomes [4]. It has been revealed that there is a decrease in the level of cytochrome C in mitochondria under the influence of malignant growth against the background of comorbid pathologies [5]. Metabolic changes remain the key stage that assists in the transformation of a normal cell into a tumor phenotype. The supply of energy in cancer cells mainly occurs by anaerobic glycolysis. To limit the flow of excess energy, the transition of cell respiration

from glycolysis to oxidative phosphorylation is a necessary step.

Therapeutic agents demonstrating anti-tumor specificity cause serious damage to normal cells, limiting in such a way their clinical effectiveness. The use of agents, which suppress or disrupt the bioenergetic profile of cancer cells, may be useful in the treatment of cancer [6]. Such methods include activation therapy [7], the use of xenon [8], and the accompanying cytochrome C therapy in the treatment of lung cancer in combination with chemotherapy drugs [9].

Despite the fact that there are a lot of studies devoted to the protective properties of antioxidants in chemotherapy, many unresolved issues remain high on the agenda. In this connection it should be mentioned that it is also important to identify their anti-carcinogenic activity and specify the optimal mode of their preventive use.

Recently medical drug Cytochrome C has been developed, which represents a high-molecular-weight iron-porphyrin compound, a conjugated protein, similar in its structure to hemoglobin (it consists of heme and a single peptide chain). Cytochrome C plays an important role in the biochemical redox processes in almost all aerobic organisms. These reactions occur with the participation of two mitochondrial enzymes: cytochrome oxidase and cytochrome reductase. Heme exhibits the properties either of an electron donor or its acceptor. It is highly reactive with oxygen radicals, such as peroxide or hydrogen peroxide, which is a strong oxidizer. Heme metabolites act as traps for the peroxide radical. Heme-containing cytochrome C is capable to neutralize free oxygen radicals in certain redox processes.

The aim herein is to study the effectiveness of the use of Cytochrome C at the early stages of the growth of Pliss lymphosarcoma in outbred albino rats.

Materials and methods

Our experimental studies were carried out in outbred albino male rats with an initial weight of 180-220 g delivered by the National Medical Research Centre of Oncology, Ministry of Health of the Russian Federation. The research in animals was conducted in accordance with the Directive 86/609/EEC on the Protection of Animals Used for Experimental and Other Scientific Purposes and Order No. 267 "Approval of the Rules of Laboratory Practice" dated June, 19, 2003 issued by the Ministry of Health of the Russian Federation. All rats were kept under the same conditions, 5 individuals in each standard plastic box, under the natural light conditions, at an ambient temperature of 22-26°C and free access to water and food. The observation of the animals was performed every day, including twice a week measurements of weight and volumes of subcutaneous tumor nodes.

The malignant process was modeled using the Pliss lymphosarcoma cell line supplied by the N. N. Blokhin Russian National Research Center at the Russian Academy of Medical Sciences (Moscow). The strain of the Pliss lymphosarcoma tumor was identified and separated by G. B. Pliss in 1960 from a female rat whose nutrition contained 3,3-dichlorobenzidine from the birth. The tumor consists of small and large irregularly shaped lymphoid cells. A high mitotic activity is noted in this case. The life expectancy of animals varies from 12 to 95 days. In our experiments, the tumor strain sample was cryopreserved, thawed and maintained by subcutaneous inoculation in outbred albino rats. The material for the transplantation was harvested from donor rats on tumor development day 16-17. In doing so, 40 outbred albino male rats were subcutaneously inoculated with the Pliss tumor strain cells. Two subgroups were separated as follows: the main test group, where the rats received experimental preventive treatment (20 animal individuals), and the reference one, where instead of the tested medication in question the animals were injected with a saline solution in the same way and in the same volume as it was the case with the tested medical drug (20 animal individuals). The experimental animals lived until their natural death. Within 1 hour after the subcutaneous transplantation of Pliss lymphosarcoma, Cytochrome C was administered intraperitoneally at a single dose of 1.6 mg/kg once a day (the maximum dosage for humans converted to rats). The drug was administered for 10 weeks according to an intermittent schedule: 5 medication days followed by a 2-day no-medication interval. Over the course of the experiment, the growth of tumors was monitored.

Statistical processing of the obtained results was carried out using the Student's parametric criterion with a PC with the STATISTICA 10.0 software and applying the nonparametric Wilcoxon-Mann-Whitney criterion test. All the results obtained were checked for their compliance with the law of normal distribution (the Shapiro-Wilk criterion). Some of the indicators were found to be in correspondence with the law,

while the others were evaluated as inconsistent therewith. For the indicators with the normal distribution, the Student's criterion was employed, and for those in disagreement with the normal distribution law, the Mann – Whitney criterion was applied. The data were presented as an arithmetic mean value ± standard error of the mean (M±m). The differences between the two samples were considered statistically significant at $p<0.05$.

Results Subcutaneous tumors were identifiable in all rats of the reference group (100%) who did not receive the medication treatment, as well as in most of the rats of the main test group (55%), who received Cytochrome C; at the same time, tumors were not identifiable in 45% of the animals in the main test group (see Table 1 herein). Against the background of the experimental medication treatment, all tumors in the rats of the main test group demonstrated their regression with time (see Tables 1-3 herein).

Moreover, in 73% of the cases, with full recovery of rats, i.e., the complete regression of the tumors was observed, and 3 rats died (27%). In dead animals, their tumors, despite their large size, became soft upon the use of Cytochrome C and were found fluctuated in palpation. When opening the tumors, their necrotic contents flowed out. In the reference group of the rats, the subcutaneous tumors grew throughout the experiment and had a dense-elastic consistency, and at necropsy the tumors had the standard appearance (see Table 1 herein).

The regression of the subcutaneous tumor nodes upon the actions and effects made by Cytochrome C has been evidenced not only by the smaller average tumor volumes in the rats of the main test group, but also by a decrease in the coefficient φ, which characterizes an average specific rate of tumor growth (see Table 2 herein). φ is an integral indicator that objectively reflects the growth of tumors during the entire observation period. It is determined by the formula as follows: $\varphi (t1, t2) = (\ln F (t2) / F (t1)) / (t2-t1)$, where F (t1) is the volume of the tumor at the beginning of the interval; F (t2) is the volume of the tumor at the end of the interval; and t2 – t1 is the time interval.

The effectiveness of the experimental medication therapy was evaluated by the percentage of the tumor growth inhibition (PTGI) and the coefficient of therapy effectiveness (γ).

By this means $PTGI = (K-Op) / K \times 100$, where K is the average volume of tumors in rats of the reference group, Op is the average volume of tumors in rats of the test group.

Table 1

Effect made by Cytochrome C on production of experimental subcutaneous tumors and dynamics of their growth in rats inoculated with Pliss lymphosarcoma

groups / indicators	Reference group (rats with a growing tumor)	Main test group with cytochrome C medication (rats with a regressing tumor)
number of rats with tumor, pc.	10	11
number of rats without tumor, pc.	–	9
number of rats/dead rats (in main test group), pc.	10 (100%)	8 / 3
time of the production of tumors (survivors/ dead), day of the experiment	7.2±0.8	11.3±2.5 / 6.8±1.2
Final volume of tumors (survivors/dead), in main test group, cm^3	92.5±9.4	23.6±4.7 / 53.8±6.1

Table 2

Change in the rate of tumor growth (φ) in rats with Pliss lymphosarcoma, arb.u. (M±m)

Day of the experiment / Group of aimals	10	13	16	20	23	27	29
Reference	1.03±0.34	1.48±0.50	0.88±0.05	0.68±0.03	0.57±0.02	–	–
Cytochrome C	0	0.77*±0.05	0.52*±0.09	0.27*±0.17	0.17 *±0.17	0.04±0.22	0.04±0.17

Note: *statistically significant difference compared with the reference

Table 3

Dynamics of PTGI and γ in rats with Pliss lymphosarcoma

Day of the experiment / Coefficients	8	10	13	16	20	23
PTGI, %	– 267.65	0	11.40	3.13	55.11	67.79
γ, arb.u.	7.50	15.63	6.77	19.27	35.99	33.14

γ = C (control, reference) / K (experiment), where K is the coefficient of change in the volume of the tumor; K = Vt / Vo, where Vt is the volume of the tumor after the therapy in the studied time; Vo is the initial volume of the tumor.

On day 8 of the experiment, the size of subcutaneous tumor nodes in the rats treated with Cytochrome C was significantly larger than the respective reference values (see Table 3 herein).

On day 10, the sizes of tumors in both groups were evaluated as follows: in the rats treated with Cytochrome C and in those without medication the sizes were found to be identical and practically did not differ from each other within 16 days of the experiment. From day 20, the tumors in the rats of the main test group began to intensively regress (see Table 3 herein). When evaluating the antitumor effectiveness of the Cytochrome C medication, it was revealed that the effectiveness of the treatment was at a minimum on day 8 and 13 of the experiment and at a maximum at the end of the observation period on day 20 and 23 (see Table 3 herein).

Apparently, Cytochrome C has produced its anti-tumor effect in different ways: in 45% of the rats, the drug immediately suppressed the development of subcutaneous tumors, and in 55% of the cases, the medication effect has been demonstrated with a delay: its anti-tumor effect is cumulative. Before a certain point in time, the subcutaneously transplanted tumors continued to grow, however when the concentration of Cytochrome C reached a certain "therapeutic" value, necrosis of the tumor cells occurred. In most of the animals, the body was able to cope with the necrotic masses and eliminate them without negative consequences: the rats demonstrated their recovery. In 3 rats, the organism was not capable to cope with the consequences of necrosis, despite the fact that the tumor tissue was lysed, it remained in the body. Finally, intoxication with the products of the tumor decay led to the death of the animals. According to the results of the study, a patent for the invention was duly obtained by our research team [10].

Conclusions

Thus, Cytochrome C, used according to the therapeutic and preventive schedule, has shown a pronounced anti-tumor effect. In 45% of the cases, the medical drug has prevented the development of Pliss lymphosarcoma, in 55% of the cases tumors have developed, but subsequently, from day 20, they have demonstrated regression, when we have recorded 73% of the animals with complete recovery and 27% with well-marked lysis of the tumor tissue. Perhaps, the effectiveness of the drug can be increased if an inert medium is used to protect the protein from proteolytic cleavage, when it enters blood, against the background of detoxification drugs. The obtained data support the reasonability of the recommendation for using cytochrome C in the complex treatment of cancer as a promising factor of the accompanying therapy.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Stellanin: a promising medical drug for accompanying therapy in lung cancer treatment

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Abstract

One of the cancer prevention measures involves the correction of the altered functions of the body's regulatory systems. Many malignant tumors are accompanied by the thyroid system dysfunction.

The aim of our study was to reveal an effect of an iodine-containing drug on the development of a tumor process in the lungs and the level of thyroid hormones in blood and the thyroid gland in male rats.

Material and methods. Outbred white male rats were divided into the following groups: a group of intact animals (n=7); a comparison group – 5 weeks after an intravenous inoculation of sarcoma 45 (S45) at 2*106 (n=7); a main group – 5 weeks after an intravenous inoculation of S45 and intragastric administration of Stellanin at a single dose of 0.4 mg/kg within an hour after the inoculation (n=10). RIA was used to determine levels of free (F) and total triiodothyronine (T3) and thyroxine (T4) in the blood serum and the thyroid.

Results. The lungs of rats in the comparison group were totally affected by the tumor, and the thyroid gland showed a sharp decrease in the levels of all hormone forms: T4 – by 18.7 times, T3 – by 8.5 times, FT4 – by 8.1 times, FT3 – by 21.3 times, while only FT4 and FT3 decreased in blood by 2.5 and 1.5 times, respectively ($p<0.05$). No tumor lesions were detected in the lungs of rats of the main group, and the hormone levels exceeded the levels in the comparison group: in the thyroid, FT4 by 3.7, T4 by 15.0 and T3 by 6.0 times; in blood, FT4 by 3.3 and FT3 by 1.7 times.

Conclusions. The effect of Stellanin inhibiting malignant growth of S45 in the lungs is accompanied by the restoration of low levels of thyroid hormones in the thyroid and blood.

Keywords

Pliss lymphosarcoma, Thyroid gland, Thyroid hormones, Rats, Stellanin drug.

Imprint

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Morbidity and mortality from malignant pathology are increasing every year all over the world [1]. Treatment of malignant neoplasms often is associated with high costs and expenditures. This makes it necessary to find new approaches to the rational use of the available health resources. Therefore, attention is paid to prevention as the main direction of the fight against cancer [2]. It is often impossible to identify external causes that contribute to the initiation of malignant pathology. Then, to prevent the development of tumors, various methods and medications are employed to normalize the altered functioning of the body. In particular, such methods include activation therapy [3], use of xenon [4] as well as chemoprophylaxis, i.e. a long-term use of a synthetic or a natural agent to avoid or exclude the formation and progression of neoplasms.

One of the measures of cancer chemoprophylaxis is the correction of the body regulatory systems functioning that has changed due to a growing tumor. It has been previously found that the performance of the hypothalamic-pituitary-thyroid system shows disorders or abnormalities in malignant pathology [5, 6]. It is known that one of the active components of the thyroid hormones, which are necessary for the proper functioning of all organs, is iodine. The specific mechanism of an action and an effect made by iodine on the body has not yet been fully clarified, but it is postulated

as to be a sophisticated integral impact, including the participation of the thyroid hormones, transforming growth factor beta-1 (TGF-β1) and iodolipids, such as iodolactone or 2-iodohexadecanal (2-IHDA) [7].

Not so long ago, medical drug Stellanin has been synthesized in Russia, the active agent of which is 1,3-diethylbenzimidazolium triiodide, incorporating an iodine and an organic component in its structure. The developer of this new medical agent is LLC Pharmpreparat (Certificate RU LSR-000161/09, dd. January 16, 2009). Previously, the antitumor effect produced by Stellanin on human cell cultures and experimental tumors in mice has been reported [8; 9]. Based on the use of Stellanin, we have elaborated our own "Method for preventing metastatic lung damage in an experiment" [10]. According to the data obtained, rat males who received Stellanin according to the preventive schedule for 8 weeks lived more than 1.5 months longer after stopping treatment; there was no tumor process in the lungs. At the same time, those rats who did not receive Stellanin died within 5-6 weeks from severe respiratory insufficiency and cachexia due to total lung damage by the tumor process.

The **aim** herein is to study the effect of the above iodine-containing drug on the development of a tumor process in the lungs and the level of thyroid hormones in blood and the thyroid gland in experimental rat males.

Materials and methods

Our experimental studies were carried out in 24 outbred white rat males with an initial individual weight of 180-220 g delivered by the National Medical Research Centre of Oncology, the Ministry of Health of the Russian Federation. The research in animals was conducted in accordance with the Directive 86/609/EEC on the Protection of Animals Used for Experimental and Other Scientific Purposes and Order No. 267 "Approval of the Rules of Laboratory Practice" dated June, 19, 2003 issued by the Ministry of Health of the Russian Federation.

All rats were kept under the same conditions, 5 individuals in each standard plastic box unit, under the natural light conditions, at an ambient temperature of 22-26°C, with free access to water and food. The animals were divided into the following groups: a group of intact animals: 7 rats; a comparison group: 5 weeks after intravenous transplantation of sarcoma 45 (C45), 7 rats; a main test group: 5 weeks after intravenous transplantation of C45 and experimental preventive treatment with 1,3-diethylbenzimidazolium triiodide, 10 rats.

Modeling the malignant process in the lungs was reproduced by the method of Sidorenko Yu. S. et al. [11]. A tumor suspension of C45 cells in saline solution (in the volume of 0.5 ml per animal, in the amount of $2 * 10^6$ tumor cells) was injected into the subclavian vein, the needle was removed, the injection site was tightly pressed for 1 minute with a cotton swab soaked in 70% alcohol with a small addition of iodine.

Within an hour after intravenous transplantation of the tumor, the rats of the main group were intragastrically administered Stellanin at a single dose of 0.4 mg/kg (the dose for humans converted for that for the rats), diluted in distilled water with a volume of 0.5 ml, according to an intermittent schedule: medication for 5 days followed by an interval for 2 days without medication; the duration of the exposure was 8 weeks. The rats from the comparison group were intragastrically injected with water in the same volume and according to the same schedule as Stellanin from day 1 [10].

The rats were decapitated 5 weeks after the tumor material was transplanted and the experimental treatment began. The study period was specified due to the peculiarities of the progression of the malignant process in the lungs in rats from the comparison group: upon expiration of 5-6 weeks, the rats died due to the total tumor lesion. Blood after decapitation of the rats was collected into dry sterile test tubes without preservatives, and serum was separated by centrifugation with a cold centrifuge at 2 thousand rpm for 10 minutes. The thyroid gland was harvested on ice using a 0.1 M potassium-phosphate buffer pH 7.4 containing 0.1% Tween 20 and 1% BSA, 10% organ homogenates were prepared. The content of free and combined forms of triiodothyronine (FT3 and T3) and thyroxine (FT4cb and T4) in serum, and homogenates was determined with the use of radioimmuneassay (test kits Immunotech, Czech Republic; analyzer Arian, Russia).

Statistical processing of the obtained results was carried out using the STATISTICA 10.0 software. The collected data were checked for compliance with the law of normal distribution (according to the Shapiro-Wilk criterion). When comparing samples with a normal distribution, the Student's parametric criterion was applied, in another case the Mann – Whitney

criterion was used. The results are presented as an arithmetic mean value ± standard error of the mean (M±m). The differences between the two samples were considered statistically significant at $p<0.05$.

Results

In the presented study, all rats belonging to the main experimental group had no signs of respiratory failure at slaughter 5 weeks upon completion of the experimental therapy with Stellanin. Upon performed necropsy, their lungs did not show differences from those found in the intact rats, and no histological signs of a tumor lesion were detected. In the rats included in the comparison group, some signs of respiratory failure were recorded in the form of dyspnea, tachypnea, intercostal retraction, cyanosis of the skin of the legs, the nose and the ears; 5 rats had nose bleeding. According to the autopsy findings, the lungs of the rats without the treatment were totally affected by the tumor nodes of a rounded shape, whitish-gray color, of different diameters, sometimes merging with each other; hemorrhages were found in the lung tissue; some patchy swollen areas of emphysema along with atelectasis regions were detected. The results obtained are found to be in agreement with those produced earlier [10].

The dynamics of the concentration of the thyroid hormones in the thyroid gland and serum in male rats with C45 intravenous transplantation with the experimental medication and without thereof is presented in Table 1 given herein.

5 weeks after the malignant process development in the lungs in the male rats from the comparison group, the level of FT4 decreased compared with the level in the intact animals: in the thyroid gland by 8.1 times and in the blood serum by 2.5 times, respectively (see Table 1 herein). Against the background of the Stellanin medication, the FT4 content in the rats of the main group was higher than that recorded in the comparison group: in the thyroid gland by 3.7 times and in the serum by 3.3 times, respectively. At the same time, the hormone content in the thyroid gland did not reach the normal values: it was 2.2 times less than the level found in the intact males, while in blood it exceeded the corresponding indicator of the intact animals by 1.6 times ($p<0.05$) (see Table 1 herein).

The amount of FT3 in serum and the thyroid gland, as well as FT4, 5 weeks after the intravenous C45 cell transplantation was lower than the levels recorded in the intact rats: in the thyroid gland by 21.3 times and in serum by 1.5 times, respectively ($p<0.05$). The experimental therapy did not change the hormone level, i.e. the amount of FT3 in the thyroid gland remained low, as it was the case with the comparison group, while the serum concentration of FT3 did not differ from the intact animal values and was 1.8 times ($p<0.05$) higher than reported for the rats without the above medication (see Table 1 herein).

In contrast to FT4, the level of which decreased in all the examined tissues in the males with a malignant process in the lungs, the T4 concentration changed in different ways: it decreased in the thyroid gland and, as a result, became 18.7 times less than the level detected in the intact rats and increased in serum, 1.5 times ($p<0.05$) exceeding the corresponding indicator in the intact animals (see Table 1 herein). Upon the effect made by Stellanin, the level of the hormone in the thyroid gland was stabilized: the concentration

Table 1

Concentration of hormones in the tissues in males with malignant lung damage and its suppression due to the Stellanin medication

Indicators and tissues / Group of rats	Thyroid gland (per g of tissue)				Serum (per litre)			
	FT4 pmol	FT3 pmol	T4 (nmol)	T4 (nmol)	FT4 pmol	FT3 pmol	T4 (nmol)	T4 (nmol)
Intact group	**34.00** ±4.73	**9.78** ±1.76	**2.06** ±0.35	**0.17** ±0.04	**18.83** ±1.12	**5.35** ±0.44	**59.33** ±4.91	**4.31** ±0.42
Comparison group	**4.20*** ±2.35	**0.46*** ±0.21	**0.11*** ±0.02	**0.02*** ±0.001	**7.56*** ±2.47	**3.51*** ±0.32	**87.84*** ±9.28	**4.71** ±0.70
Main group	**15.43*,+** ±1.18	**0.79*** ±0.22	**1.67+** ±0.46	**0.12+** ±0.03	**24.98*,+** ±1.10	**5.87+** ±0.37	**100.86*** ±7.92	**4.94** ±0.21

Note: Statistically significant differences: *relative to the values of intact males; + relative to the values of males in the comparison group with a tumor lesion of the lungs.

of T4 did not differ from the value found in the intact animals, and it was 15.2 times higher than that in the males without treatment. However, the blood level of T4 in the rats of the main group remained as high as that found in the rats from the comparison group, and at the same time it was 1.7 times ($p<0.05$) higher than the value recorded in the intact rats (see Table 1 herein).

The content of T3 in the blood serum did not change in either case: against the background of the tumor growth and upon completion of the above experimental therapy. While the production of the above form of the hormone in the thyroid gland was reduced against the background of the development of the malignant process in the lung, the amount of T3 in the rats from the comparison group was 8.5 times less than that reported for the intact rats. In the rats of the main group treated with Stellanin, the level of T3 in the thyroid gland did not differ from the values found in the intact animals and, therefore, was 6.0 times higher than that in the rats from the comparison group (see Table 1 herein).

Discussion

A decrease in the concentration of free forms of thyroid hormones in blood, namely, hypotriodothyroninemia and hypothyroxinemia, detected in rats 5 weeks after the transplantation of malignant cells into the subclavian vein, has indicated the formation of the "low T3/T4" syndrome, often concomitant with malignant pathology. It is noted that this syndrome is diagnosed with cancer of the breast, the lungs, the thyroid gland, the kidneys and other organs and is evidence for the severity of the improper condition, due to a pronounced disorder in the functioning of the hypothalamic-pituitary-thyroid axis [12; 13]. The pathophysiological basis for the development of this syndrome is an intensive "consumption" of thyroid hormones by malignant tissues with the development of the so-called abnormally consumption-related hypothyroidism. This is evidenced not only by low levels of free forms of triiodothyronine and thyroxine in blood, but also by a deficiency of thyroid hormones in the thyroid gland.

It has been found that thyroid hormones contribute to the neoangiogenesis and proliferation of malignant cells of many tumors [14]. The direct stimulating effect produced by the thyroid hormones on the proliferation of neoplastic cells "in vitro" is revealed with respect to lung adenocarcinoma, breast and prostate cancer. An interesting fact is that only thyroxine, but not triiodothyronine, administered externally, contributes to the development of the Lewis lung carcinoma as an experimental tumor in mice, whose malignant growth has been suppressed under hypothyroidism. Moreover, the stimulating effect of thyroxine is mediated not by direct stimulation of the Lewis carcinoma cells, but by enhancing neoangiogenesis through plasma membrane integrin avß3 [15].

The depletion of the thyroid hormone synthesis by the thyroid gland might be attributed to the intense central stimulation thereof. This is evidenced by an increase in the specific weight of the hypothalamus, where, as is known, the synthesis of thyrotropin-releasing hormone occurs, that has been identified by us in parallel studies. A low level of free forms of thyroid hormones in blood may enhance the hypothalamic synthesis of thyrotropin-releasing hormone according to the negative feedback principle. The sex hormones as well as IGF-I and VEGF may also stimulate the production of thyroxine in the thyroid gland [16].

In our experiments, intragastric administration of the organic iodine drug has suppressed the development of sarcoma 45 in the lungs in the rats. It is assumed that the mechanism of the antitumor action and effect made by Stellanin thereon at the molecular level is associated with the restoration of the functional activity of mitochondria, suppressed in a significant number of the tumor cells, and as a result, the initiation of the process of apoptosis of the oncotransformed cells [8;9;17]. However, iodine contained in 1,3-diethylbenzimidazolium iodide can be captured directly by the cells of the thyroid gland and modify the performance of the latter, which has been deteriorated under the progression of the experimental malignant process in the lungs.

We have found that 5 weeks after the start of experimental therapy Stellanin has inhibited the reduction of free forms of thyroid hormones in blood, as well as FT4 and combined forms of the thyroid hormones in the thyroid gland, typical for the development of a malignant process in the lungs without treatment. In other words, the synthetic activity of the thyroid gland has been restored in the rat males upon the effect produced by Stellanin, and the "low T3/T4" syndrome has been neutralized that bears witness to the normalization of the thyroid axis of the regulation. Apparently, the normalization of low levels of FT3 and FT4 in

blood in the animals under the influence made by Stellanin according to the negative feedback principle "has eliminated" the central pituitary stimulation of the thyroid gland, which takes place at the stages of the formation of the tumor process in the lungs.

Thus, the effect made by Stellanin, which suppresses the malignant growth of C45 in the lungs, is accompanied by an elevation of low levels of thyroid hormones in the thyroid gland and blood. It is advisable to carry out further preclinical research of Stellanin aimed at its subsequent use in the accompanying therapy of patients with oncological pathology who have a risk of developing malignant lung damage.

Statement on ethical issues

Animal studies were carried out in compliance with the principles of humanity, which are set out in the European Community Directive (86/609 / EEC) and the Declaration of Helsinki. The study was approved at a meeting of the bioethical committee for work with animals of the Federal State Budgetary Institution "National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation dated January, 28, 2013, protocol of the ethical committee No. 3/3. All authors participating in the study signed informed consent to participate in the study.

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Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Myoendocardial formations of heart atria and ventricles of the female Amur leopard cat (Prionailurus bengalensis euptilurus) in normal fertile age

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Abstract

The object of the study is the hearts of four young reproductive females of the Amur leopard cat, a rare mammal representative of the cat family. The animal is untamed and lives only in the wild. The material was selected during the autopsy according to generally accepted methods. The age of the studied individuals of the Amur leopard cat was determined taking into account the data; the internal structure features of the heart were studied. Earlier, we described the morphometric parameters of different age groups male hearts. The heart of the studied individuals is slender, ellipsoid in shape; the myoendocardial formations of the atria have a well-defined ridge-like structure. The walls of the ventricles are characterized by pronounced trabeculation. The papillary and trabecular complex includes: trabeculae carneae of varying intensity, depending on the localization on the wall; septomarginal trabeculae that have their own distinctive features in the right and left ventricles; main and additional papillary muscles. The septomarginal trabeculae of the right ventricle have a pronounced muscular structure; the corresponding formations of the left ventricle are thin, tendon-like, significantly exceeding the first in length. The most pronounced papillary muscles are localized in the left ventricle. Papillary muscles of the right ventricle are expressed slightly, with the exception of the parietal muscles.

Keywords

Heart, Morphometric parameters, Internal structures, Amur leopard cat

Imprint

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Introduction

The research is devoted to the morphology study of rare animals' organisms that is of high importance in the field of natural science disciplines. The heart, being a vital organ that ensures functioning of the body, is always relevant for the specialists in the field of morphology, anatomy, cardiology, etc. The heart of the Amur leopard cat is a little-studied one, it is a small and vulnerable subspecies of small cats living in the wild and protected by law.

Over a long period of time, we have accumulated material on the heart structure of certain species representing the fauna of the Primorsky taiga. We have identified four young females of the Amur leopard cat of the fertile age (11-12 months). There are data on the structure of the heart of sexually mature individuals of this subspecies, but they belong to males [1, 3]. Processing the material we were also guided by the works of other scientists who are building their research in the field of morphology of the cardiovascular system [4–7, 9, 11].

The purpose is to study and systematize the morphometric parameters of the heart and internal structures of the female Amur leopard cats.

Materials and methods. The research was conducted in the Animal Diseases Diagnostic Center of the Federal State Budgetary Educational Institution of Higher Education "Primorskaya State Agricultural Academy". The heart structure dissection of four Amur leopard cat females was studied and measured, it was prepared by means of removal from corpses, release from blood clots and a heart sac.

The work with the organ was carried out according to generally accepted instructions, all the methods are fully described in the abstract of the author's thesis [1].

Research results. The location of the organ in the chest is at the level from the third to the seventh rib, the longitudinal axis relative to the chest bone is in the range of 29-31°.

The heart mass in the studied animals was 27.88±1.94 g, the relative mass of the organ was 0.5%.

The thickness of the walls of the right heart: the ventricle – 2.61±0.23; the atrium – 0.58±0.11 mm. Similar parameters of the left half: the ventricle – 6.07±0.33; the atrium – 0.65±0.13 mm. The heart of the Amur leopard cat is slender, the organ index in all the studied animals was up to 65%, which corresponds to an oval shape (see Figure 1 herein).

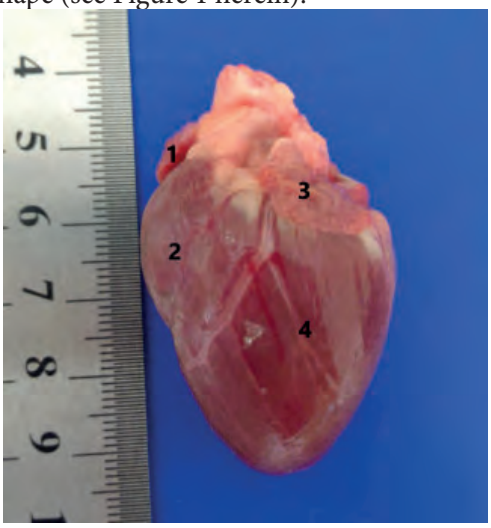

Figure 1. The heart of an adult female Amur leopard cat: 1 – right atrial appendage; 2 – the right ventricle; 3 – left atrial appendage; 4 – the left ventricle

The atria are different in size: auricle of the right atrial appendage is larger, has dimensions of 36.78±0.91 by 19.95 mm, is located above the entire upper surface of the corresponding atrium; auricle of the left atrial appendage is more compact, its parameters are 18.75±0.42 by 15.11±0.44 mm.

The internal structures of the atria are represented by a terminal crest, from which m.musculi pectinati of the first and second orders and coronary sinus branch. In the right atrium, m.musculi pectinati is more pronounced, more numerous and more extended than similar formations of the left atrium (see Figure 2 herein).

The heart of the Amur leopard cat is distinguished by a well-developed left ventricle, and less a right one.

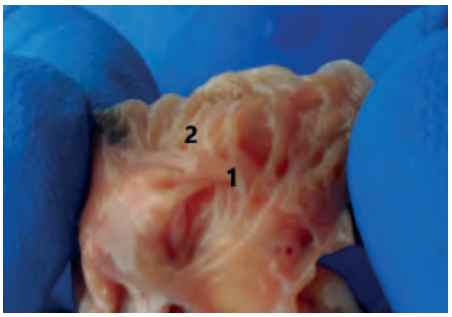

Figure 2. Myoendocardial formations of the right atrium: 1 – m.musculi pectinati of the first order; 2 – m.musculi pectinati of the second order

Table 1

Morphometric parameters of the m.musculi pectinate of the heart atria of the Amur leopard cat, mm; M±m

Atria	Right atrium		Left atrium	
Indices (m.musculi pectinate)	I order	II norder	I order	II order
Quantity, pcs.	5-6	16-18	2-3	9-10
Length, mm; M±m	5,9±0,96	5,2±0,27	5,1±1,53	5,0±0,24
Width, mm; M±m	2,1±0,23	1,0±0,67	2,7±1,00	1,1±0,8

The internal architectonics of the ventricles differs in the number and size of structures, but is uniform and is represented by a papillary and trabecular complex consisting of trabeculae carneae, septomarginal trabeculae, papillary muscles, as well as coronary tendons and cusps of atrioventricular valves. The binding function is performed by tendinous cords.

The trabeculae carneae consists of moderator band (trabecular) and intersection, having different intensity relative to their localization. So, in the right ventricle, their distribution is approximately the same over the entire surface, but on the medial wall they have a smooth relief. At the same time, the same elements on the medial wall of the left ventricle are the most pronounced and large. The size and number of these structures are shown in Table 2.

Table 2

Morphometric parameters of trabeculae carneae of the heart ventricles of the Amur leopard cat; mm; M±m

Index		Left ventricle			Right ventricle		
		Length (mm)	Width (mm)	Number (n)	Length (mm)	Width (mm)	Number (n)
Cranial wall	Trabecula	6,1±0,87	1,5±0,35	4	7,5±1,02	1,5±0,18	7-8
	Intersection	1,0±0,08	0,7±0,31	3	1,7±0,37	1,0±0,12	4
Caudal wall	Trabecula	6,3±0,7	1,3±0,24	5	7,1±1,31	2,0±0,6	4
	Intersection	1,3±0,13	10±0,17	4	1,1±0,35	0,7±0,24	4
Medial wall	Trabecula	7,7±0,65	1,4±0,74	7-8	7,2±0,45	1,9±0,31	7-8
	Intersection	1,4±0,34	0,7±0,32	7-8	1,4±0,24	0,7±0,19	5-6

An important element of the trabecular system of the ventricles is a complex of septomarginal trabeculae, which are tendon or muscle "bridges" that lie at the base of the main papillary muscles and connect them to the interventricular septum. In all the studied individuals, these formations are well expressed, there is a significant pattern in their organization: in the left ventricle, they are thin tendinous bands with branching at the place of attachment to the surfaces of the endocardium. The size of the septomarginal trabeculae of the specified ventricle is: cranial – 9.12±2.11 by 0.5±0.11 mm; caudal – 7.01±0.74 mm. The septomarginal trabeculae of the right ventricle differ significantly, they are quite powerful, short muscle formations, and attachment to the surfaces is complete by the entire surface of the adjacent formation. Dimensions: the cranial length is 2.55±0.54 mm, the diameter is 1.63±0.63 mm; the caudal length is 2.2±0.53, the width is 1.44±0.25 mm.

However, the caudal septomarginal trabecula, which lies at the base of a large parietal muscle is additional to papillary muscle and is not always detected. In one case, out of four, the specified muscle was missing together with the corresponding septomarginal trabecula.

Papillary muscles are large myoendocardial formations of the ventricular cavity. In the right ventricle of the Amur leopard cat, these formations are the most numerous, but they are small in size (see Figure 3 herein).

Figure 3. The right ventricle of the Amur leopard cat: 1 – m.papillaris magnus; 2 – m.papillaris parvi; 3 – m.papillaris subarteriosus; 4 – cranial septomarginal trabecula; 5 – trabeculae carneae (intersection); 6 – trabeculae carneae (trabecula) 7 – tendinous cords

There are three main papillary muscles in the right ventricle: *a large* one (m.papillaris magnus) lies on the cranial wall, cylindrical in shape, connects to the interventricular septum by means of the cranial septomarginal trabecula; *a hyparterial* one (m.papillaris subarteriosus) is a septum, cone – shaped, looks like a small swelling on the cranial wall; *a small* muscle (m.papillaris parvi) belongs to the caudal wall of the ventricle, also cone-shaped. We identified up to two additional papillary muscles, both septal and parietal, they were observed in 75% of the studied animals.

In the left ventricle, two papillary muscles are located on the wall of the ventricle (see Figure 4 herein).

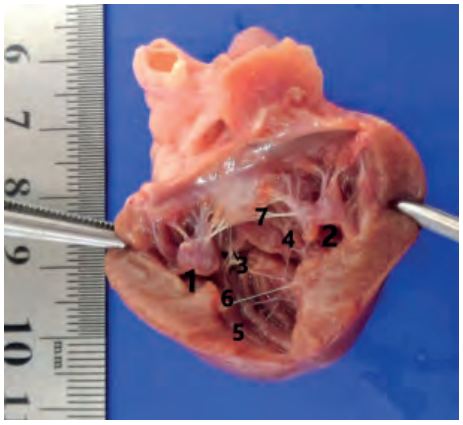

Figure 4. Left ventricle of Amur leopard cat: 1 – m.papillaris subatrialis; 2 – m.papillaris subauricularis; 3 – cranial septomarginal trabecula; 4 – caudal septomarginal trabecula; 5 – trabeculae carneae (trabecula); 6 – trabeculae carneae (intersection); 7 – tendinous cords

M.papillaris subatrialis, lying at the base on the cranial wall, is large, cylindrical in shape with two heads at the top. *Musculus papillaris subauricularis*, which belongs to the caudal wall, is similar in structure to m.papillaris subatrialis, longer, but smaller in diameter. In 25% of cases, the presence of three heads was detected, in 75% there are two heads. The dimensional data of these myoendocardial formations are presented in Table 3 herein.

Conclusions. Summing up our research, we can provide the following conclusions:

1. The heart of the Amur leopard cat is slender, with a developed left ventricle, and a relatively weak right one.

2.The trabecularity of the myoendocardial formations of the atria and ventricles is well expressed, which indicates a high contractility of the heart, since the studied animal is an active predator. This feature can also be traced in other representatives of wild cats [2, 7, 10].

3. The septomarginal trabeculae of the right and left ventricles differ in their structure: in the first they

Table 3

Morphometric parameters of papillary muscles of the right and left ventricles of the Amur leopard cat, mm; M±m

Right ventricle			Left ventricle		
Name of the papillary muscle	Length (mm)	Width (mm)	Name of the papillary muscle	Length (mm)	Width (mm)
m.papillaris magnus	7,7±1,61	2,1±0,81	m. papillaris subauricularis	11,2±1,75	4,8±0,75
m.papillaris parvi	3,8±0,48	2,7±0,29	m. papillaris subatrialis	10,4±3,21	5,1±0,41
m.papillaris subarteriosus	2,9±1,32	1,7±0,19	-	-	-
Additional parietal	5,9±0,97	1,8±0,66	-	-	-

are short strong muscle structures, in the left they have a tendon type of structure, relatively long, branching at the place of attachment to the walls. The function of both is to prevent overstretching of the ventricular walls during their contraction [4].

4. The papillary muscles of the right ventricle have a cone-shaped and cylindrical shape, the largest of them are parietal. The left ventricular papillary muscles are cone-shaped with the splitting of the tops into smaller formations – heads. Their size varies slightly.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REVIEW

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Use of Laser Technologies in Oncourology

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Abstract

Due to the increasing use of laser technologies in oncourology, we consider it relevant to publish a review of domestic and foreign articles for 2015-2021. The range of application of various lasers in oncourology is very wide (holmium (Ho): YAG, thulium (Tm): YAG, etc.). In comparison with traditional surgical interventions, the greatest effectiveness of laser technologies in combination with endoscopy is clearly traced, the risks of intra – and postoperative complications are minimized, the period of inpatient stay for patients changes.

Keywords

Oncology, Urology, Laser, Holmium laser (Ho): YAG, Thulium laser (Tm): YAG

Imprint

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Introduction

Since the middle of the XX century, the era of an introduction and a wide use of laser technologies in medicine began. 1960 has offered the greatest scientific discovery: the world's first laser [1]. The scope of the first application of the lasers in urology and oncology included lithotripsy and laser bladder surgery [2, 3]. The morphology and histology of laser-exposed tissues was first described by Staehler et al. in 1976. The laser in surgery of the 80s already demonstrated many "points of application" [4, 5]. The pioneering resection of prostate adenoma was performed with laser in 1986 [6] and found its broad application since 1990 [7]. The evolution of laser technologies and the accumulation of experience in their use in medicine gave an impetus to the development of a large number of types of lasers [8]: KTP (potassium titaniyl phosphate, KTP: Nd: YAG); LBO (lithium borate, LBO: Nd: YAG); diode laser; holmium lasers (Ho): YAG (with aluminoy yttrium garnet); thulium lasers (Tm): YAG.

The aim of our reference literature review is to analyze and compare the different types of lasers used in the treatment of urology and onco-pathologies.

Benign hyperplasia and malignant tumors of the prostate

Among the various lasers, with a wavelength approximately of 2 μm, the most effective are found those with crystalline media based on aluminum yttrium garnet activated by chromium, holmium and tullium ions. It has been just the holmium that laser in the fifteen-year period, since 2002, has been massively introduced in use in urology and uro-oncology in the Russian Federation [15]. In the process of refining of urological endoscopic techniques, it has been detected that with a laser pulse, water quickly evaporates directly at the distal end of the optical fiber, which is characterized by the absence of heating and burning of the fiber tip. In this case, 20% of the energy is consumed for water evaporation, and the rest thereof can be successfully used for the purpose of surgery. A tissue dissection is performed with a contact-type technique, and coagulation is provided in a contact-free way. The radiation of this laser mainly evaporates blood, and upon the exposure thereof the blood vessels can be twisted without noticeable formation of blood clots that reduces the probability of a secondary bleeding due to their mechanical disintegration [15]. With the use of this technique providing an interaction of laser with the tissues of the posterior urethra and the ablation of prostate tissues, scarring is practically avoided during the healing of a laser wound [14]. The microscopy examination of histological samples, 7 days after exposure to a holmium laser with an energy density of 310 and 530 J/cm^2, has revealed moderate edema associated with some hemorrhage fields, mixed inflammatory cell infiltration in the region of coagulation necrosis [13]. The areas of the prostate close to the region of coagulation necrosis are expanded prostatic ducts partially filled with

protein-eosinophilic secretion products and zones of necrotic epithelial cells thoughout the entire depth of the cut. The interstitial stroma, between the expanded ducts and the glands, is characterized by moderate swelling with multifocal mononuclear infiltration. By week 3 (after exposure to the holmium laser), the area of the crater-type destruction is covered with epithelium consisting of 2–6 layers thereof. In the tissue areas close to the laser cut, infiltrates from inflammatory cells, neutrophils, lymphocytes and macrophages are determined throughout the depth of the produced cut. In the same areas noted are the glands overfilled with cellular detritus, with obliterated ducts. 5 weeks after the completed laser destruction, the exposed areas are covered with normal transitional cell epithelium. Morphological changes of this sort has not initiated the cicatricial process [3, 12]. With the beginning of the use of the thulium laser (Tm): YAG (2017), the negative effects of the holmium laser, i.e. the damaging effect made by the shock wave on the soft tissues, the retropulsion (practically the absence thereof) of the stone during fragmentation, the use in practice of only rigid technique, have been eliminated.

Surgeons have faced the problem of false negative results in the diagnostics of prostate cancer after transurethral laser enucleation (laser destruction of the edges of resection). This problem was often discussed by foreign researchers in publications released in 2017-18. The main difficulty in the diagnostics of prostate cancer in the study of histological material is the damaging effect of the laser and the impossibility of objective histological verification of tissues of the resection margins [9]. It should also be noted that the diagnostic value of transurethral interventions for the detection of malignant prostate lesions is low. In order to verify the diagnosis in patients with a high risk of prostate cancer, it is advisable to perform a preliminary transrectal multifocal prostate biopsy [16]. Laser ablation/resection of the prostate in cancer is not an effective or safe alternative to radical prostatectomy.

Malignant tumors in the urinary system

The laser technique has shown its good performance and applicability particularly in the treatment of urothelial carcinomas. In 2017 (Huazhong University of Science and Technology, Wuhan, China, Department of Urology of Tongji Clinic), a comparison of the effectiveness and feasibility of laser enucleation of a bladder tumor with transurethral resection was published in 13 studies [10]: 1037 patients underwent transurethral resection of prostate (TURP), and 975 underwent transurethral laser enucleation. According to database studies available before 01.2017 (PubMed, Wed of Science, Google scholar and Medline, EMBASE), there were no significant differences in the surgery time between the two groups, although laser enucleation was superior to the TURP in bladder perforation, in the catheterization time, in the reduction of the obturator nerve block reflex, hospitalization time and the recurrence rate per annum. A more accurate result of histological studies of the removed tissue during laser resection is noted [10]. In 2018, the AMC University Clinic (Amsterdam, the Netherlands), Prof. O. Lodeizen, has published data on the treatment of patients with prostate cancer with focal laser ablation [2]. Her report has highlighted the difficulty of using the laser ablation accompanied by extremely high cost of equipment and the lack of advantages in comparison with conventional radiation treatment methods.

Experts of the Spanish University Hospital named after J. M. Morales Meseguer, Murcia, presented their experience of outpatient treatment of recurrent bladder cancer by transurethral laser fulguration followed by outpatient MMC (mitomycin-C instillation [11]. This technique is considered to be a real and safe alternative to transurethral resection of the bladder.

Conclusions

Laser technologies, almost everywhere, have become an integral part of medical practice throughout the world. They have found their application in the treatment of urolithiasis, benign prostatic hyperplasia, oncopathology and scarring of the urinary system. When using a laser in performing a surgical intervention, it is noted the following:

– the surgery time is reduced;

– the number of bleedings, intra - and postoperative complications decreases;

– there is no damaging effect made by the shock wave on the tissue in the application area available;

– it is possible to use various in instrumentation considering its calibration and rigidity (flexibility in use).

The practice of using conventional surgical instruments is inferior in efficiency to methods of laser technologies in endoscopy and laparoscopy. Perhaps, in the near future, these newer technologies will successfully compete with radical resection surgery in tumor disease treatment and urological pathology.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Liriodendrin, ameliorates hypertension by calcium channel blockade and enhancing enos expression in wistar rats

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Abstract

Introduction: Hypertension is found to be the prime cause of death worldwide in spite of a number of available treatments which suggests that there is a need of discovering new lead molecules that would be more effective to treat cardiovascular disease (CVD). Liriodendrin, the lignan phytoconstituent possesses potential pharmacological effects. Literature survey suggests that liriodendrin could be effective in mitigating hypertension considering its structural similarity with reported cardiovascular protective drugs. Hence liriodendrin is investigated to reveal its mechanism of actions to support its antihypertensive property.

Methods: Hypertension was induced in male wistar rats with DOCA salt. Hypertensive rats were treated with liriodendrin for 4 weeks. Blood pressure, heart rate, body weight, lipid profile, serum nitrite levels, vascular reactivity to various catecholamines, in-vitro calcium channel blocking assays, antioxidant assay, determination of aortic calcium level, endothelial function, expression of eNOS analysis were studied.

Result: Liriodendrin was found safe orally up to 2000 mg/kg. It showed a significant decrease in heart rate, blood pressure and mean arterial pressure. In-vitro study on the isolated rat aorta revealed the calcium channel blocking potential of liriodendrin. Vascular reactivity to various catecholamines was normalized. Vascular endothelium was significantly protected by the enhanced release of nitric oxide and eNOS expression by the western blot technique. Oxidative stress was also significantly reduced.

Conclusion: Liriodendrin was found to be beneficial in hypertension as it produced vasorelaxation by blocking calcium channels, enhancing nitric oxide release, and reducing oxidative stress. Thus, liriodendrin may be useful to relieve hypertension and cardiovascular complications.

Keywords

DOCA, Hypertension, Endothelial dysfunction, Oxidative stress, Liriodendrin

Imprint

Anjali B.Tajanpure, Vandana S. Nade, Laxman A. Kawale. Liriodendrin, ameliorates hypertension by calcium channel blockade and enhancing enos expression in wistar rats. Cardiometry; Issue 20; November 2021; p. 47-59; DOI: 10.18137/cardiometry.2021.20.4759; Available from: http://www.cardiometry.net/issues/no20-november-2021/liriodendrin-ameliorates-hypertension

Introduction:

Hypertension is becoming the prime cause of death worldwide. According to the survey, the ubiquity of hypertension is stable but no improvement in disease state has been observed. Reasons for such condition may be due to the lack of awareness, increase in financial burden [1] or poor control over hypertension with the available treatments [2, 3]. Natural products and the traditional medicines are the great source of biodiverse phytoconstituents [4]. Hence, such phytochemicals can be investigated to develop new lead moiety which would be safe, effective and an alternative to present treatment, in ameliorating various diseases and disorders.

Lignans are the secondary metabolite found in number of plant parts like seeds, legumes, whole grains, fruit, and vegetables [5,6]. Chemically they are classified into eight structural subgroups [7]. Generally, lignan get metabolized to enterodiol, enterolignan and enterolactone [8]. Enterolactone has been found to act as an antioxidant against human LDL oxidation [9] and has an antidiabetic action too [10]. Lignans has also been reported to inhibit the activation of calmoduline dependent enzyme cyclic nucleotide phosphodiesterase [11], platelets activating factor [12], antagonize calcium channels and enhances nitric oxide synthesis (NOS) [13].

Liriodendrin is found in plants like *Linum usitatissimum, Acanthopanax senticosus, Boerhaavia diffusa, Sargentodoxa cuneata, Kalopanax pictus* etc [14]. It possesses similar pharmacophore as that of Matairesinol, which is a reported calcium channel antagonist [15] and calmoduline inhibitor. The fused bicyclic ring of liriodendrin may be useful as it may produce umbrella like effect on target calcium channels, causing blockade of channels (Fig. 1). As a result, the goal of this study was to investigate the pharmacological actions of liriodendrin in a preclinical model in order

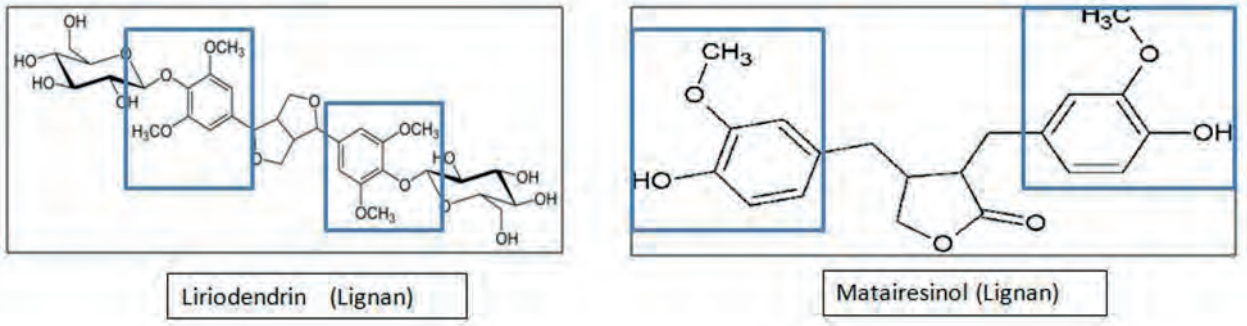

Figure 1. Liriodendrin-and-matairesinol-structural-similarity

to determine its therapeutic potential in hypertension, so that the information gathered may be used in future clinical trials.

Material and Methods:

Procurement of animals and chemicals

Total fifty one male wistar rats (*Rattus norvegicus*) weighing 150 - 200 g and age 4-6 weeks were obtained from LACSMI Biofarms Pvt. Ltd. Pune. They were housed in polypropylene cages with husk bedding, under 12:12h light dark cycle. Room temperature was maintained at around 25 ± 3°C. Rats were fed with commercial pellets rat chow and water was provided *ad libitum*. Animals were housed for two weeks before being used in tests that followed the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), based in New Delhi, India. The animal study was approved by institutional animal ethics committee (IAEC/2018/06).

Liriodendrin with chemical name (2S,3R,4S,5S,6R)-2-[4-[6-[3,5-dimethoxy-4-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxyphenyl]-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]furan-3-yl]-2,6-dimethoxyphenoxy]-6 (hydroxymethyl) oxane-3,4,5-triol, Product number SMB00181 and lot no. 122228321V was procured from Sigma Aldrich with purity of 97 %.

In-vitro calcium channel inhibition assay

The descending rat aorta was isolated and cleaned with adhered connective tissues. The aorta was cut into 3-5 mm wide rings, and then rings were mounted in the organ tube of student's organ bath. One side of aortic rings were tied to a frontal lever (isometric) and other end to aerator tube. For 20 minutes, the aortic rings were incubated in a calcium-free Krebs solution containing 0.5 mmol/l EDTA and 40 mmol/L KCl. The rings were then incubated for 20 min with vehicle or liriodendrin (30 µmol/l) respectively and concentration response curves were recorded by cumulatively adding $CaCl_2$ (0.1-3.0 mmol/L)[16].

Acute oral toxicity study of liriodendrin

Oral acute toxicity study was performed by UP and Down method (OECD 425) on female wistar rats. First three rats were dose with 175 mg/kg of liriodendrin. As no mortality was observed within 48 hour, next dose was increased to 550 mg/kg. No toxicity and mortality was observed within 48 hours. So limit dose of 2000 mg/kg was given to another three rats. All the animals were observed for any abnormal changes for 14 days. After14th day, The rats were euthanized and anatomical and morphological alterations were observed.

Induction of hypertension

For four weeks, male wistar rats were given Deoxycorticosterone acetate (20 mg/kg, s.c.) twice weekly with olive oil A 1% NaCl solution was used in place of drinking water [17].

Experimental design

Animals were divided in eight groups each containing 6 animals. **Group 1:** Vehicle (Olive oil 5 ml/kg); **Group 2:** Treatment Control 1 (Liriodendrin 2.5 mg/kg, p.o); **Group 3:** Treatment Control 2 (Liriodendrin 10 mg/kg, p.o); **Group 4:** Disease control (DOCA 20 mg/kg, s.c twice a week for 4 week); **Group 5:** DOCA + Liriodendrin (2.5 mg/kg, p.o); **Group 6:** DOCA + Liriodendrin (5 mg/kg, p.o); **Group 7:** DOCA + Liriodendrin (10 mg/kg, p.o); **Group 8:** DOCA + Nifedipine (10 mg/kg, p.o). The liriodendrin treatment lasted for 28 days. All animals were sacrificed by cervical dislocation at the conclusion of the investigation.

Heart rate and systolic blood pressure

Non-invasive systolic blood pressure and heart rate were recorded by using tail-cuff method (PowerLab Data Acquisition system). While for invasive blood pressure, animals were anaesthetized by Ketamine and Xylazine (75 mg/kg and 15 mg/kg, i.p. resp.). Animal's limbs were fixed on the experimental table and incision was given at the neck region to open up the trachea. About 4 cm of left carotid artery was exposed and cleaned it free of any connective tissues and vagus nerve. The carotid artery was cannulated using a polypropylene cannula, with the other end attached to a blood pressure transducer on the AD Instruments Power Lab Data Acquisition system. After that, the systolic blood pressure, mean arterial pressure, and heart rate were determined [18].

Serum Lipid Profile

Serum total cholesterol, triglyceride and HDL were determined by biochemical autoanalyzer (Model-BL 200, Elico) using standard biochemical kits (Agappe diagnostic, Mumbai).

Serum Nitrite level

100 µl serum sample was collected from each group and to it 10 µl (0.2 U/ml) aspergillus nitrate reductase (sigma aldrich cat. no. 72548), 25 µl (50 mM) HEPES buffer, 25 µl (5µM) FAD and 50 µl (0.1 mM) NADPH was added and incubated for 30 min. To the incubated mixture, 5 **µl** of potassium ferricyanide (1500 U/ml) and 50 µl of 100 mM pyruvic acid was added and then was incubated for 10 min. Finally, 1 mL of premixed griess reagent (HiMedia laboratories) was added and incubated for 10 minutes before colorimetric measurement was used to determine absorbance at 543 nm [19].

Calcium level in aorta

Calcium level in aorta was determined by using ab102505 calcium assay kit. Initially standard curve was determined with concentration 0, 0.4, 0.8, 1.2, 1.6 and 2µg calcium/well. Animals were sacrificed and 50mg of aorta was weighed and washed with cold phosphate buffer solution. The tissue was suspended in 1000µl of cold calcium assay buffer and was cold centrifuged at 15000rpm. The supernatant was collected for analysis. The first six microplate wells were filled with 50 µl of standard calcium dilutions. Previously prepared tissue homogenate was added in other wells with sample volume 50 µl. Then 90µl of chromogenic reagent followed by 60µl of calcium assay buffer wad added in each well. The plate was then incubated at room temperature for 10 min. and then absorbance was recorded by microplate reader at OD575 nm (BMG labtech, Spectrostar^{nano}).

Catecholamine-induced vascular reactivity

Ketamine and Xylazine (75 mg/kg and 15 mg/kg i.p.) were used to anaesthetize the rats in each group. For drug administration, a tiny polyethylene catheter was cannulated into the right jugular vein. Blood pressure (BP) was measured directly from the left common carotid artery using a pressure transducer. The mean change in BP to adrenaline (1 g/kg/ml), noradrenaline (1 g/kg/ml), and phenylephrine (1 g/kg/ml) was collected using the PowerLab Data Acquisition System after 30 minutes of stabilisation [20, 21].

Evaluation of integrity of the endothelium

Descending rat aorta was isolated and placed in Krebs solution. Aortic rings of nearly 3 mm length were prepared and mounted on organ bath containing 15 ml of Krebs solution at 37^0C and aerated with 95% O_2. The rings were suspended between two stainless-steel hooks, one of which was attached to the end of a bathing tube and the other to a force transducer (PowerLab® **ML750), to record contractions.** The resting tension of 1 g was applied to preparation and equilibrated in a 15 ml bathing solution for 60 min. The rings were then exposed to 1×10^{-6} M Phenylephrine. When the contractile response of Phenylephrine was plateaued, acetylcholine was added in a cumulative fashion. The concentrations of acetylcholine were prepared in range of 1×10^{-9} to 1×10^{-5} M [22, 23].

Determination of eNOS expression by western blot technique

The rat heart from vehicle, treatment control, disease control, DOCA + liriodendrin (10 mg/kg) group and standard group were isolated, washed and were homogenized in lysis buffer. 50µg of protein from each group was loaded separately on 7.5 % polyacrylamide SDS gel (Bio-Rad. Corp) for separating desired protein by gel electrophoresis. After completing the run, separated proteins from polyacrylamide-SDS gel was transferred to nitrocellulose paper (Bio-Rad. Corp) in glycine-methanol buffer. To prevent nonspecif-

ic contact, the nitrocellulose membrane was blocked with TBS–milk before being incubated overnight with the maine NOS antibody (Bio-Rad. Corp). The membrane was rinsed three times with TBS the next day, then incubated for three hours with a secondary antibody conjugated with alkaline phosphatase. The membrane was then cleaned again and developed with NBT as the substrate in an alkaline buffer (Alkaline phosphatase substrate kit, Bio-Rad. Corp). Densitometry analysis was performed to evaluate the extent of gene expression with liriodendrin treatment [24, 25].

Antioxidant assay

The aorta from the vasorelaxation studies was used for the preparation of aortic homogenate. The aorta was weighed after being washed with isotonic saline. In ice-cold 0.1 M phosphate buffer, a 10% (w/v) tissue homogenate was produced (pH 7.4). Centrifugation of the homogenate at 1000 rpm for 20 minutes at 40 ^{0}C yielded the post nuclear fraction for the catalase assay; centrifugation at 12000 rpm for 60 minutes at 40 ^{0}C yielded the post nuclear fraction for the other SOD and LPO assays. The following assay was performed with a bio-spectrophotometer (Model-BL200, Elico).

a. Catalase activity

The H2O2 breakdown was detected at a wavelength of 240 nm. The assay mixture consisted of 3 ml of H2O2 in phosphate buffer (pH7) and 0.05 ml of tissue homogenate supernatant (10%), and the change in absorbance was measured at 240 nm after 1 minute. The enzyme activity was calculated using the millimolar extinction coefficient of H2O2 (0.07/mmol/cm). Micromoles of H2O2 decomposed per minute per milligram of protein were used to calculate the results. [26, 27].

b. Superoxide dismutase

The activity of superoxide dismutase (SOD) was measured using the Kono technique. The SOD prevented the reduction of nitrobluetetrazolium (NBT), which was measured spectrophotometrically at 560 nm. In a nutshell, the reaction was started by adding hydroxylamine hydrochloride to a reaction mixture containing NBT and the homogenate's post nuclear fraction (10 percent). The results were expressed as unit per milligram of protein, with one unit of enzyme defined as the amount of SOD required to inhibit the rate of reaction by 50 % [28].

c. Lipid peroxidation (LPO)

The quantitative measurement of lipid peroxidation in the rat aorta was performed according to the method of Wills. The amount of malondialdehyde formed was measured by action with thiobarbituric acid at 532 nm. Reaction mixture contains: 0.1 ml tissue homogenate, sodium lauryl sulphate (SLS), 20% acetic acid, and thiobarbituric acid. Mixture was heated at 95°C for 1 h. Then n-butanol and pyridine mixture was added. Absorbance was measured at 532 nm of the upper layer (organic layer). The results were expressed as nanomoles of MDA per milligram of protein using extinction coefficient 1.56×10^5/M/cm [29].

Determination of ROS in rat heart using 2', 7'- dichlorodihydrofluorescein diacetate.

Rat heart from each group was isolated and was homogenate in 50 mM phosphate buffer solution at 10,000 x g for 20 min at room temperature. To the 5ml of homogenate, 2.5 µl of 2 mM 2', 7'-dichlorodihydrofluorescein diacetate (HiMedia Laboratories Pvt Ltd) dissolved in ethyl alcohol was added. The mixture was incubated on shaker at room temperature in dark room for 1 hour. Test sample was analyzed by fluorescence spectrophotometrically (Systonic S-915 Fluorimeter) with emission wavelength at 485 and detection wavelength in range of 500–600 nm. Fluorescence was measured in terms of emitted fluorescence intensity [30].

Statistical Analysis

All the observations are presented as mean ± SEM. The data is analyzed by student t-test (paired) and One-way ANOVA followed by Dunnett's test. $^{*/\#}$ signifies $P < 0.05$, $^{**/\#\#}$ signifies $P < 0.01$, $^{***/\#\#\#}$ signifies $P < 0.001$.* and ns (non-significant) indicates comparison with disease control group (DOCA salt). # and $ (non-significant) indicates comparison with vehicle group. Graph Pad Prism 5.0 version statistical software was utilized.

Results

In-vitro calcium channel inhibition assay

The maximum contraction in CRC of $CaCl_2$ when treated with vehicle was obtained at 3.5mMol/l. Treatment to same aorta with liriodendrin showed reduction in maximum contraction by 34.1%. The reduction was significant ($P < 0.001$) as compared to vehicle. The observation suggest that, liriodendrin has blocked Ca^{+2} influx (Fig. 2). The graph has shifted parallel towards right as compared to normal CRC which signifies the presence of competitive antagonism (Fig. 3).

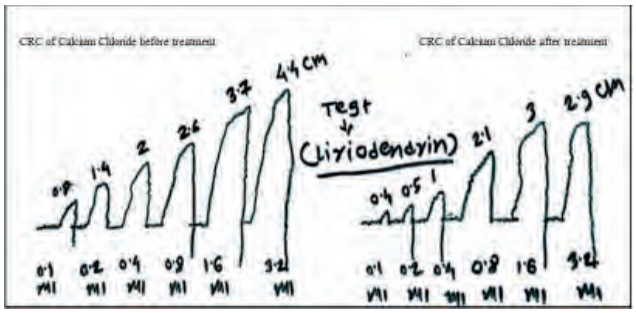

Figure 2. CRC of calcium channel blocking assay

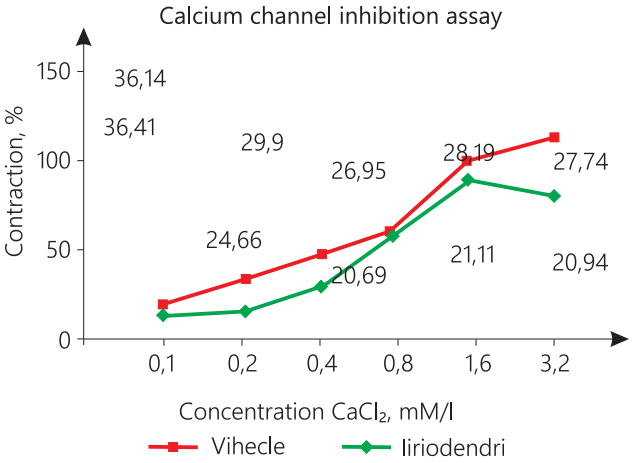

Figure 3. % Contraction Vs Conc. of calcium chloride

Acute oral toxicity study of liriodendrin:

The rats showed no any abnormal behavioural changes like awareness, mood, motor activity, CNS excitation, posture muscle tone and autonomic responses. Anatomy and morphology of vital organs like liver, brain, heart, lung, kidney, pancreas and spleen and relative organ weight was found normal. The LD_{50} was found to be greater than 2000 mg/kg (Table 1a and 1b).

Table 1a.

Acute toxicity study of Liriodendrin- behavioural examination.

Sr. no	Parameters	1st day	7th day	14th day
A	**Awareness**			
1	Alertness	Increased	Normal	Normal
2	Visual placing	Normal	Normal	Normal
3	Passivity	Normal	Normal	Normal
B	**Mood**			
1	Grooming	Reduced	Normal	Normal
2	Vocalization	Normal	Normal	Normal
3	Restlessness	Increased	Normal	Normal
C	**Motor activity**			
1	Reactivity	Normal	Normal	Normal
2	Spontaneous activity	Normal	Normal	Normal
3	Touch response	Normal	Normal	Normal
D	**CNS excitation**			
1	Startle response	Moderate	Nil	Nil
2	Tremors	Nil	Nil	Nil
3	Convulsion	Nil	Nil	Nil
E	**Posture**			
1	Body posture	Normal	Normal	Normal
2	Limb position	Normal	Normal	Normal
F	**Muscle tone**			
1	Grip strength	Normal	Normal	Normal
G	**Autonomic**			
1	Pupil size	Normal	Normal	Normal
2	Skin colour	Normal	Normal	Normal
3	Piloerection	Nil	Nil	Nil
4	Salivation	Nil	Nil	Nil
5	Urination	Normal	Normal	Normal

Table 1b

Acute toxicity study of Liriodendrin_ relative organ weight.

Sr. no	Weight	Liriodendrin		
		175 mg/kg	550 mg/kg	2000 mg/kg
1.	Liver	2.44 ± 0.01	2.65 ± 0.12	2.40 ± 0.16
2.	Brain	0.8 ± 0.1	0.8 ± 0.04	0.80 ± 0.06
3.	Heart	0.48 ± 0.03	0.50 ± 0.07	0.47 ± 0.02
4.	Lung	0.64 ± 0.02	0.72 ± 0.03	0.64 ± 0.04
5.	Kidney	0.70 ± 0.02	0.77 ± 0.04	0.69 ± 0.05
6.	Pancreas	0.14 ± 0.01	0.19 ± 0.03	0.15 ± 0.02
7.	Spleen	0.20 ±0.04	0.21 ± 0.06	0.20 ± 0.01
8.	Total body	177.0 ± 4.62	179.7 ± 4.91	182 ± 2.019

Body weight

The treatment with DOCA salt showed significant increase in body weight as compared with vehicle group. While normalization of body weight was observed in all liriodendrin treated groups and nifedipine group. ($P < 0.001$) (Table 2).

Systolic blood pressure and heart rate

The non-invasive blood pressure was determined using tail cuff. The group 4 showed significant rise in systolic blood pressure as compared to vehicle. Group 5 showed no significant change in blood pressure while higher doses of liriodendrin (5 and 10 mg/kg) showed significant ($P < 0.05$) decrease in blood pressure as compared to group 4.

The systolic blood pressure was also elevated with treatment of DOCA salt by increasing extracellular and plasma volume as compared to vehicle group when measured by invasive method. Liriodendrin

treatment showed moderately significant ($P < 0.01$) reduction in group 5 and 6, while group 7 and 8 has shown most significant ($P < 0.001$) reduction in blood pressure as compared to DOCA group.

Mean arterial pressure was raised in diseased control group and found to be normal in treatment control group as compared to vehicle group. Group 7 and 8 showed maximum reduction in MAP ($P < 0.001$), while group 6 showed moderate lowering of MAP ($P < 0.05$) as compared to disease control group. No significant change was observed in group 5.

Heart rate with the treatment of DOCA was increased significantly as compared to vehicle. But no significant reduction was observed in any of the liriodendrin group and nifedipine as well (Table 3).

Serum lipid profile

Diseased control group 4 showed significant rise in serum cholesterol levels were found as compared to vehicle group. No change was observed in treatment control groups when compared to vehicle group. While liriodendrin treated groups showed significant reduction ($P < 0.001$) in serum cholesterol levels as compared to DOCA salt treatment (Table 2).

Serum triglyceride levels were significantly elevated in group 4 while no significant changes were observed in group 2 and 3 as compared to vehicle group. Group 7 showed moderate ($P < 0.01$) reduction while group 8 exhibited most significant ($P < 0.001$) reduction in triglyceride levels. No significant changes were observed in group 5 and 6 (Table 2).

Serum HDL levels were significantly lowered in group 4,while no significant elevation in serum HDL was observed in liriodendrin treated groups and nifedipine group (Table 2).

Determination of serum nitrite level

Serum nitrite level was significantly lowered in disease control group as compared to vehicle group ($p < 0.001$). Treatment control group 3 showed sig-

Table 2
Effect of liriodendrin on body weight and lipid profile.

Treatment	Body weight	Total cholesterol	Triglyceride	HDL
Group 1: Vehicle	208.0 ± 2.55	105.8 ± 5.93	99.23 ± 1.82	58.20 ± 3.96
Group 2: Treatment control 1	200.3 ± 3.43$^{\$}$	99.7 ± 2.01$^{\$}$	101.2 ± 1.23$^{\$}$	61.1 ± 4.01$^{\$}$
Group 3: Treatment control 2	210 ± 0.18$^{\$}$	110.3 ± 1.21$^{\$}$	125.3 ± 2.42$^{\$}$	50.36 ± 2.04$^{\$}$
Group 4: DOCA (20mg/kg)	286.8 ± 3.52$^{\#\#\#}$	260.9 ± 4.10$^{\#\#\#}$	211.01 ± 2.12$^{\#\#\#}$	45.00 ± 2.12$^{\#\#\#}$
Group 5: DOCA + lirio (2.5 mg/kg)	257.2 ± 4.77**	214.4 ± 5.10***	198.11 ± 1.5$^{6\ ns}$	49.00 ± 2.04^{ns}
Group 6: DOCA + lirio (5 mg/kg)	245.0 ± 1.14***	212.9 ± 5.68***	186.20 ± 3.2$^{4\ ns}$	46.00 ± 2.19^{ns}
Group 7: DOCA + lirio (10 mg/kg)	241.0 ± 1.14***	2.19.6 ± 5.89***	168.20 ± 3.34**	50.20 ± 3.12^{ns}
Group 8: DOCA + Nifedipine	225.0 ± 2.16***	139.6 ± 6.34***	121.30 ± 1.43***	51.80 ± 2.27^{ns}

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

Table 3
Effect of liriodendrin on blood pressure and heart

Treatment	Non-invasive B.p	Invasive B.p	Mean arterial pressure	Heart rate
Group 1: Vehicle	117 ± 5.40	100.6 ± 4.60	90.60 ± 2.62	369.2 ± 20.67
Group 2: Treatment control 1	105.0 ± 3.43$^{\$}$	99.1 ± 2.06$^{\$}$	95.32± 1.32$^{\$}$	350.4 ± 10.22$^{\$}$
Group 3: Treatment control 2	110.2 ± 1.39$^{\$}$	99.4 ± 1.24$^{\$}$	89.8 ± 0.78$^{\$}$	355.8 ± 22.34$^{\$}$
Group 4: DOCA (20mg/kg)	157.6 ± 2.87$^{\#\#\#}$	166.6 ± 5.26$^{\#\#\#}$	118.8 ± 2.96$^{\#\#\#}$	495.2 ± 24.24$^{\#\#}$
Group 5: DOCA + lirio (2.5 mg/kg)	148.4 ± 2.34^{ns}	150.2 ± 2.40**	112.6 ± 1.43^{ns}	416.0 ± 17.01**
Group 6: DOCA + lirio (5 mg/kg)	141.6 ± 3.26*	145.2 ±1.23**	109.0 ± 0.32**	431.6 ± 19.38**
Group 7: DOCA + lirio (10 mg/kg)	140.3 ± 2.11*	138.3 ± 2.79***	105.2 ± 1.85***	450.4 ± 18.39**
Group 8: DOCA + Nifedipine	132.4 ± 3.06***	121.4 ± 2.96***	93.4 ± 0.81***	426.4 ± 24.78**

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

nificant increase in serum nitrite level suggesting enhanced nitric oxide synthesis i.e. by value $p < 0.05$. Lower dose of liriodendrin didn't showed any significant change as compare to disease control group, but group 6, 7 & 8 showed very significant increase in nitrite levels as compare to group 4 ($p < 0.001$) (Fig 4).

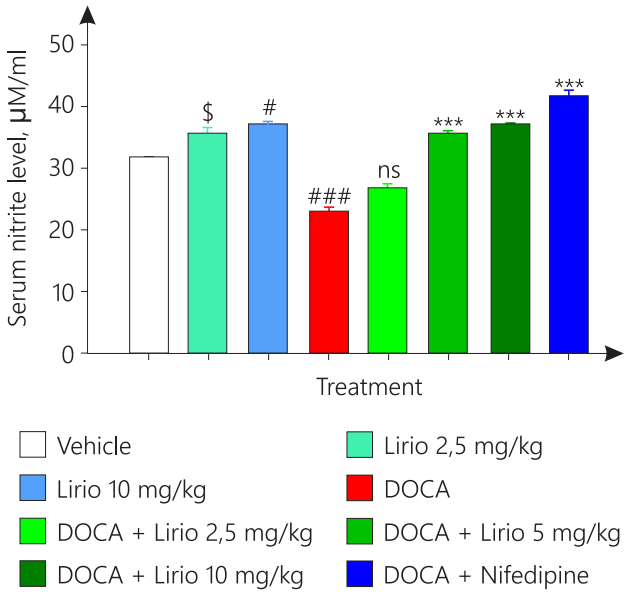

Figure 4. Serum Nitrite level

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

Calcium level in aorta

The standard curve of calcium showed linear regression which ensured precision and accuracy of measurement (Fig 5a). Aortic calcium level in DOCA salt group was significantly increased ($p<0.001$), while group 2 & 3 showed no significant change as compared to vehicle. Treatment with moderate and high dose of liriodendrin and standard showed significant ($p<0.001$) reduction in calcium level. Effect of low dose of liriodendrin was non-significant as compared to disease control group (Fig 5b).

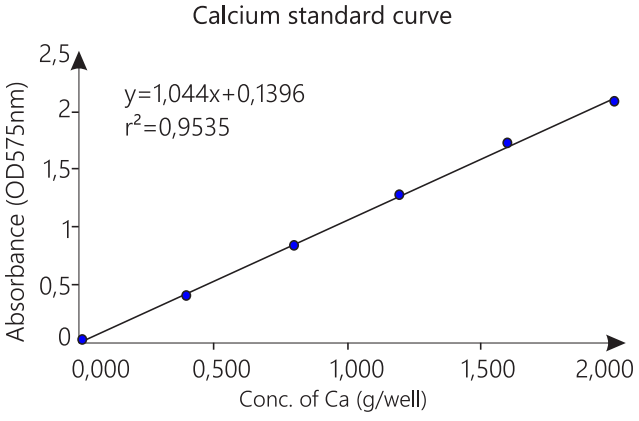

Figure 5a. Standard curve of calcium

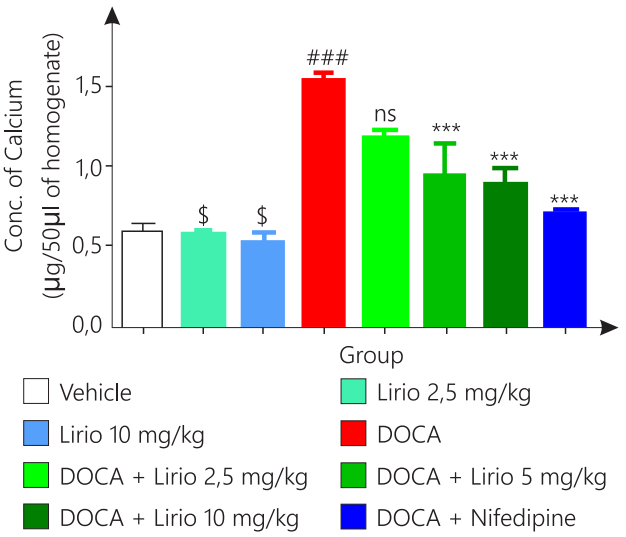

Figure 5b. Concentration of calcium in rat aorta

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

Vascular reactivity to catecholamine:

The pressor response to adrenaline, noradrenaline and phenylephrine were significantly increased ($P < 0.001$) in DOCA salt induced hypertensive rats as compared to vehicle which confirmed the endothelial dysfunction. The values of treatment control showed no variations as compared to vehicle group.

In response to adrenaline, all liriodendrin treated and nifedipine group showed significant decrease ($P < 0.001$) in pressor response as compared to group 4.

Noradrenaline and phenylephrine have more pronounced effect on blood vessels. Group 4 aorta showed prominent rise ($P < 0.001$) in blood pressure in response to noradrenaline and phenylephrine as compared to vehicle. Group 5 showed moderate decrease in blood pressure ($P < 0.01$). Group 6, 7 and 8 showed significant ($P < 0.001$) decrease in pressor response as compared to group 4 (Fig. 6).

Effect on integrity of endothelium

DOCA treated group showed significant ($P < 0.05$) reduction in vasorelaxation as compared to vehicle group. Treatment control group showed vasorelaxation same as that of vehicle group so no significant change was seen between both the groups. Group 7 and 8 showed significant relaxation ($P < 0.05$) as compared to group 4 (Fig. 7).

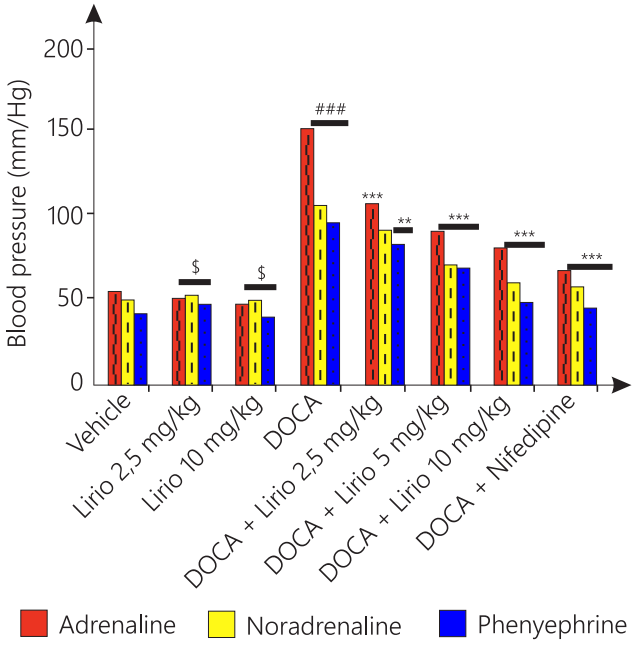

Figure 6. Vascular reactivity to catecholamines

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

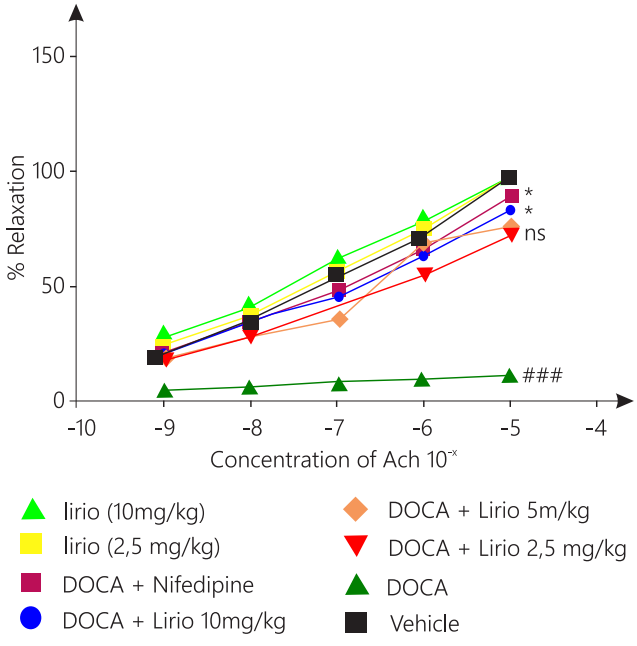

Figure 7. Ach induced vasorelaxation

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

Determination of eNOS expression by western blot technique.

DOCA salt treated hypertensive rats showed significant ($p<0.001$) down regulation of eNOS protein in heart tissue while liriodendrin alone did not showed any significant change as compared to vehicle group. Hypertensive rats treated with liriodendrin increased the expression of eNOS as compared to diseased control rat significantly ($p<0.01$). Nifedipine treated group showed most significant ($p<0.001$) increase in expression of eNOS as compared to disease control group (Fig. 8).

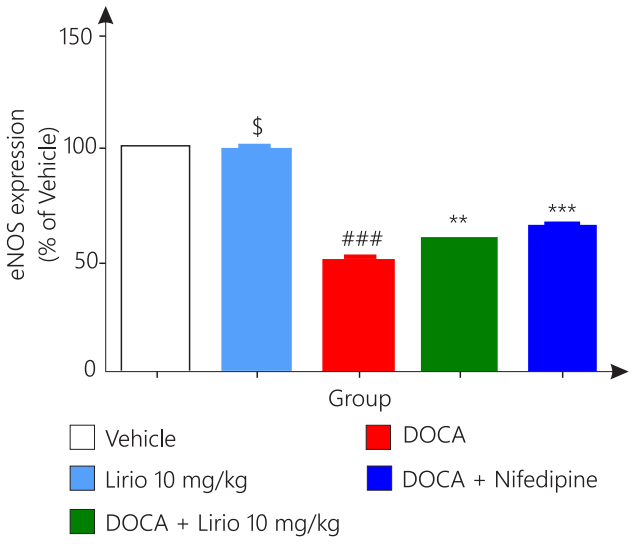

Figure 8. eNOS expression

Group 2, 3 and 4 is compared with vehicle while group 4 and 5 is compared with diseases control group.

Antioxidant assay

DOCA salt treatment developed significant oxidative stress in rats as compared to vehicle group. Treatment control group showed no any changes in antioxidant level as compared to vehicle group. Group 5 and 6 showed no significant effect on antioxidants like SOD and CAT levels as compared to group 4. While group 7 ($P < 0.01$) and 8 ($P < 0.001$) showed significant rise in antioxidant enzyme levels.

Lipid peroxidation was increased in DOCA group as compared to vehicle. Group 7 and 8 showed significant reduction in lipid peroxidation while other group showed no significant reduction in LPO as compared to group 4 (Table.4).

Determination of ROS in rat heart using 2', 7'- dichlorodihydrofluorescein diacetate.

Antioxidant effect of liriodendrin in heart tissue homogenate was performed using 2', 7'- dichlorodihydrofluorescein diacetate. Diseased controlled group showed significant ($P<0.001$) increase in fluorescence as compare to vehicle group indicating generation of oxidative stress. Liriodendrine treated group with 5mg/kg, 10mg/kg and standard group showed significant lowering in oxidative stress as compared to disease control group (Fig. 9).

Table 4

Effect of liriodendrin on oxidative stress.

Treatment	SOD (% inhibition)	CAT (μM H2O2 consumed)mg protein / min	LPO (nM MDA) mg protein
Group 1: Vehicle	83.30 ± 2.20	8.44 ± 0.42	9.27 ± 0.48
Group 2: Treatment control 1	82.1 ± 1.1$^{\$}$	9.02 ± 0.29$^{\$}$	9.9 ± 0.21$^{\$}$
Group 3: Treatment control 2	85.2 ± 0.4$^{\$}$	9.23 ± 0.57$^{\$}$	10.25 ± 1.23$^{\$}$
Group 4: DOCA (20mg/kg)	49.7 ± 4.05$^{###}$	4.23 ± 0.29$^{###}$	16.69 ± 0.93$^{###}$
Group 5: DOCA + lirio (2.5 mg/kg)	53.9 ± 3.77^{ns}	4.31 ± 0.23^{ns}	16.1 ± 1.29^{ns}
Group 6: DOCA + lirio (5 mg/kg)	59.1 ± 2.47^{ns}	5.12 ± 0.27^{ns}	14.5 ± 1.01^{ns}
Group 7: DOCA + lirio (10 mg/kg)	64.3 ± 1.67**	6.5 ± 0.26***	10.8 ± 0.39***
Group 8: DOCA + Nifedipine	74.1 ± 1.41***	7.3 ± 0.32***	9.6 ± 0.44***

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

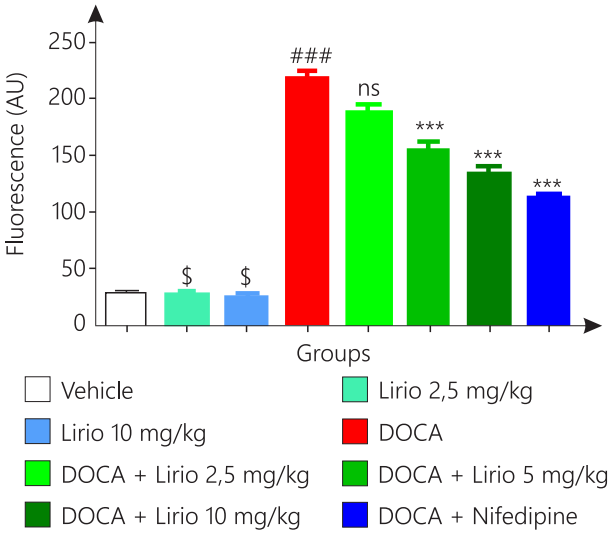

Figure 9. Antioxidant assay

Group 2, 3 and 4 is compared with vehicle while group 5, 6, 7 and 8 is compared with diseases control group.

Discussion

Liriodendrin possesses similar pharmacophore as that of Matairesinol, which has already been reported to be a calcium channel antagonist [15]. Hence it was hypothesized that liriodendrin will be beneficial in the treatment of hypertension and endothelial dysfunction.

In-vitro studies revealed that, liriodendrin blocks the voltage gated calcium channels. This outcome promoted to perform *in-vivo* study, which was performed by DOCA salt induced hypertension model in wistar rats.

Oral acute toxicity study by Up and Down method was performed for 14 days, which revealed the LD_{50} > 2000 mg/kg. Considering the toxicity study and previous research work (Jung et al., 2003), dose of liriodendrin for treatment was selected as 2.5 mg/kg, 5 mg/kg and 10 mg/kg.

Body weight is considered as a vital indicator in any pathology. DOCA salt increases the release of aldosterone, which improves sodium and water reabsorption. Increase in water level leads to weight gain. The DOCA salt group showed a considerable rise in body weight, which is in line with earlier research. While the weight of liriodendrin treated animals were increased but in a normal pattern as compared to DOCA salt treated group. Probably enterolactone, the metabolite of liriodendrin would have reduce the calorie intake by stimulating fat breakdown and boosting the growth of friendly gut bacteria [31].

In comparison to the DOCA-treated group, liriodendrin therapy significantly reduced systolic blood pressure and mean arterial pressure. The possible mechanism, by which blood pressure was thought to be reduced, was by blocking the calcium channels and restoring the endothelium. Also the lignans are found to reduce the viscosity of blood and protects the blood vessels from thickening [32]. Dyslipidaemia is the triggering cause of hypertension and other cardiovascular complications. The total cholesterol in DOCA salt treated rats was significantly increased in previous study due to inhibition in activity of HMG-CoA reductase enzyme [33]. The current study found the same thing. Liriodendrin and standard treatment significantly reduced the elevated total cholesterol levels as compared to diseased control group.

Triglyceride is transported to blood from liver through VLDL. Further Lipoprotein lipase hydrolys-

es triglycerides and converts VLDL to ILDL. Reason for elevated triglyceride levels in hypertensive rats, is might be due to increased VLDL level and decreased activity of lipoprotein lipase enzyme which was consistent with previous studies [35, 34].Liriodendrin has significantly reduced the triglyceride probably due to enhanced enzyme activity and reduced oxidative stress. Role of liriodendrin on these enzymes is unknown and need to explore.

According to Touyz et.al, the DOCA salt reduces Ca ATPase which causes decrease in efflux of Calcium [35].Also increase in permeability of plasma membrane due to hypertension was observed in the previous study. Hence in total, the elevated intracellular calcium leads to increase in PVR and so the blood pressure. Blood pressure was significantly reduced with liriodendrin. The reduction in intracellular calcium reported in this study offered significant evidence for liriodendrin's calcium channel blocking capability.

Exogenous catecholamine imparts pressor response due to sympathetic nervous system stimulation, transient increase in blood pressure is settled by release of endothelium based vasorelaxant [36]. Dysfunctional endothelial cells fail to respond to exogenous and endogenous trigger. When compared to the disease control group, the Liriodendrin-treated groups demonstrated a significant reduction in blood pressure. The effect could be due to endothelial cells releasing nitric oxide in response to vasoconstriction. This indicates that the endothelium layer has been spared injury. In addition, reduced oxidative stress and lipids might have reversed the endothelial dysfunction.

Acetylcholine is responsible for activation of nitric oxide synthase due to which the nitric oxide level increases and hence causes vasodilatation [37]. In response to ACh, a higher dose of liriodendrin caused the most vasorelaxation, indicating that the endothelium layer was protected from damage, resulting in increased nitric oxide release. While diseased control group showed no vasorelaxation might be due to reduced expression and functioning of NOS which is observed in endothelium dysfunction [38].

Nitric oxide is an unstable vasoactive gas, which quickly get oxidized to nitrate. NO metabolite, nitrate was converted to nitrite using nitrate reductase and was estimated. Decrease in serum nitrite level in disease control group indicates insufficient NO production resulting from endothelial dysfunction. While increase in nitrite levels in liriodendrin treated group reflects that Nitric oxide level was enhanced suggesting restoration of endothelial health [39, 40].

In present study, it was found that, decrease in NO level in hypertensive rat is due to downregulation of eNOS protein. Probable reason for downregulation of protein may be due to increase in ROS and uncontrolled elevated B.P. This finding indicates that the disease condition has affected the integrity of endothelium which is congruous with previous studies [41]. Liriodendrin has increased the eNOS expression. This confirms that liriodendrin possess potential to increase the nitric oxide level in heart and contribute to ameliorate hypertension.

Imbalance in free radicals and antioxidants levels in body develops malfunctions in normal physiology. Antioxidant effect of liriodendrin was determine in rat heart by using 2', 7'-dichlorodihydrofluorescein diacetate dye by fluorescence spectroscopy. ROS generated inside the cells oxidizes the dye to highly fluorescent form 2', 7'-dichlorofluorescein which is detected [30]. More the ROS formed, more the fluorescence is generated. In the present study disease control group showed maximum fluorescence indicating generation of oxidative stress. Liriodendrin group significantly reduced the oxidative stress generated by DOCA salt confirming the antioxidant potential of liriodendrin.

Antioxidant effect of liriodendrin was also studied in descending thoracic aorta. Assay was performed using nitrobluetetrazolium, thiobarbituric acid and hydrogen peroxide. Significant improvement in antioxidant levels i.e. superoxide dismutase, catalase and lipid peroxidation with liriodendrin treatment was observed. This revealed that the oxidative stress created by DOCA salt treatment might have reduced by liriodendrin by enhancing antioxidant levels, which scavenges free radicals.Further research is needed to explore the benefits of higher dose of liriodendrin. Gene expression and bioavailability studies will make the finding utilize clinically.

Conclusion

Liriodendrin has potential to antagonize the voltage gated calcium channels and reduce oxidative stress. It is also found promising in protecting endothelium which ultimately improved nitric oxide release (Fig.10). Thus, liriodendrin has beneficial effect in hypertension, further detail mechanisms need to explore to establish the possible therapeutic application of liriodendrin.

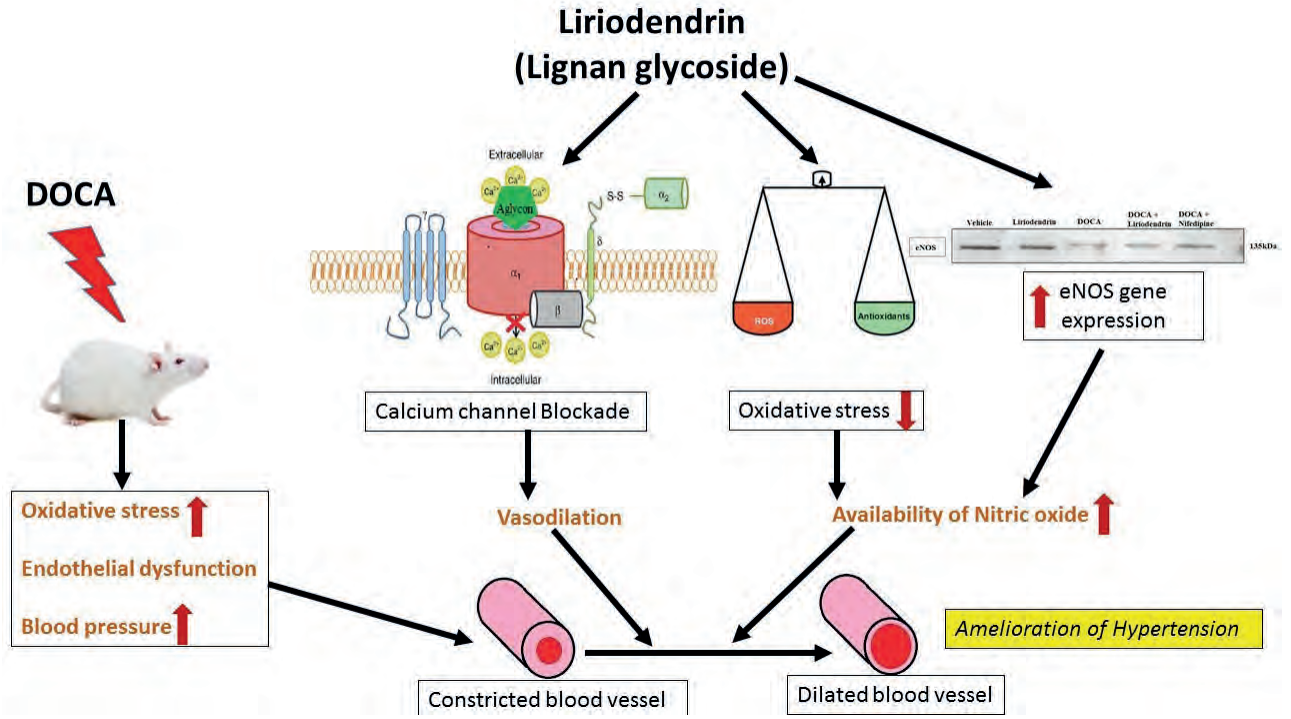

Figure10. Mechanism of action of liriodendrin

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Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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A study of perceptions about healthy food advertised in select urban areas in India

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Abstract

The percentage of the obese and overweight population in India has alarmingly increased over the last few years. It is described as a global epidemic that needs to be controlled. The two main reasons for obesity and overweight are lack of physical activity and lack of balanced diet. Childhood Obesity leads to many chronic diseases in adulthood if not cured. With the lifestyle change, physical activity has gradually decreased; therefore, a balanced diet is necessary to fight obesity. Obesity can also be controlled among the youth so that it is not carried forward in adulthood. Consequently, it is imperative to know what makes them buy products that claim to be healthy. Advertisers use the central or peripheral route of advertising to endorse the products and add labels as heuristic cues to help buyers make a healthy choice. A questionnaire that was given to the sample to understand their perception of food products that claim to be healthy indicated that the influence of celebrity brand endorsers varies with categories of food products. It also indicated that all labels do not influence the buyer. The buyers who claimed to check nutrient facts of the products also perceived the products to be healthy. Government guidelines have been established for nutritional claims made by the advertisers, but more information needs to be given to the buyers so that they can make an informed decision.

Keywords

Health claims, Heuristic cues, Perceived health quality, Brand endorsers, Labels, Brand image, Peripheral route of advertising, Central route of advertising.

Imprint

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Introduction

"An imbalance in energy intake and expenditure causes the body to accumulate and store unhealthy amounts of fat tissue, leading to obesity. The build-up of excess body fat causes health problems like breathlessness, increased sweating, joint pain, fatigue and may lead to future complications like heart diseases, reproductive problems and several other sorts of cancer." [1]. Body Mass Index (BMI) is a tool that is used commonly to measure obesity. It is calculated as the "ratio of weight, in kilograms, to height squared, in meters. Adults with a BMI of 25 or higher are classified as overweight, and those classified as obese have a BMI of 30 or more" [1].

Overweight and obesity may be avoided by a careful choice of healthy foods and frequent physical activity. In low revenue and middle-income nations, particularly in metropolitan areas, an issue that has been widespread in countries with high incomes is rising. "In 2014, there was overweight of more than 1,9 billion people (aged 18 and older) and 41 million infants under age 5. Nearly half of the overweight or obese children under the age of five resided in Asia in 2014. "In 1999-2016, the prevalence of obesity among men and women quadrupled and became a new issue." [2].

Since "very highly-processed, energy-densely low-cost meals and foods have gotten considerably cheaper. People consume caloric, fatty, sweet and savory foods while not eating enough fruits, vegetables, and pulses. Although individual nutritional requirements vary with age, gender, lifestyle, and physical activity, certain general features of a balanced diet for adults are present. The WHO lays out these guidelines. A healthy balance of nutrients, such as protein, carbs, fathers, etc., should be emphasized concerning calorie consumption and diets.

The quality and the amount of protection rely on the amino acid combination and the body's digestion and use of the protein.

Carbs offer many dietary energies and are primarily used in meals with high fiber vitamins and minerals as unprocessed complex carbohydrates. Simple carbohydrates in foods or beverages should be free to supply a maximum of about 10% of the overall calories. Additional health benefits are provided when free sugar is reduced to less than 5% of the total calorie intake –

corresponding to around 25 g or six levels teaspoons of sugar per day for a person with healthy body weight.

Fats (no more than 30 percent of total calories in consumption) should be eaten in moderation, mainly unsaturated fats.

Salt from processed foods should be below 5 grammas daily, including salt.' 1989.

Food labels "help consumers who want to follow the dietary guidelines and make healthy food choices that best fit their dietary needs by giving information about the product.» In India, FASSI has set specific rules about claims and advertisements that the food business operators have to abide by regarding their food products. Part III, section 4 of Food Safety and Standards (Advertising and Claims) Regulations, 2018 has set definitions and guidelines for nutrition claims, synonyms which may be used for allegations defined in these regulations, health claims, health claims for Fortified Food articles, and use of certain words or phrases in their schedule I, II, III, IV, and V respectively. Certain documents Discussed in the paper «Influence on healthy foods by consumers, the concept of a healthy diet, and personal values» «Healthy eating directives did not have significant links with perceived dietary quality, whereas healthy/unhealthy eating had good impacts on perceived dietary quality because individuals have confidence in a government program for their definitions of healthy eating. They found that healthy eating campaigns, focused on optimizing nutritional values, in particular, cannot successfully promote healthy eating behavior, except in addition to other opinions on healthy eating.»In Findings from [6], a new global 'FATitudes' study by American corporation Cargill state that about 70% of the Indian consumers check for fat and oil in packaged food, while globally, the figure stands at 69%. Furthermore, the survey notes that «54 percent indicated that packaged goods with fat-related labels, such as free fat, reduced fat, etc., are more likely to be bought.

Moreover, in most countries, an organic label certification affects purchase decisions more compared to non-GMO checks.» Book titled 'Conversation about Healthy Eating' argued that many people don't think in terms of processed and unprocessed and might not have the right idea about which food are healthy and which are not. People who believe that they are making a healthier choice by picking something labeled «low fat» would not check the actual contents to see if the product has low sugar or not, leads to the point that there are several misunderstandings about which foods are healthy and which aren't [7].

In a scenario like this, where a potential pandemic of obesity threatens the world and overweight and growing awareness has pushed a few people to pick healthy food, it is essential to understand how healthy food is advertised and subsequently perceived by the consumers.

Review of literature

Research conducted to prove "how the effect is closer to better and less healthy meals if they both are available" revealed that "a healthier food than a lower food, its proximity and that of competing less healthy foods are not substantially influenced." On the contrary, its closeness has affected the chance of consuming less healthful meals." [3] 'The basic case scenario provides for a 4.5 percent drop in total consumption from 80.5 minutes per week to nil in TV food advertising for US kids. In the event of a 4.5 percent lower body weight per 10 percent drop in intake, children will weigh around 2.1 percent below the present average condition results in a 0.38 kg m 2 drop in a mean BMI, with a 2.7 (95% uncertainty interval 2,3–3.1), percentage point decrease in boy prevalence and 2.4 (2.1–2.8) decrease in girl prevalence. There would be a reduction in the proportion of children with overweight." [4]Junk Consumption of food in both rich and developing economies is a key source of childhood obesity "as a worldwide epidemic. Since childhood obesity typically continues into maturity, the danger of serious health illnesses will grow an increasing number of people." [11] Past study demonstrates that the perceived quality of consumer diets is "reflective of their dietary behavior," in which intake of fruits and vegetables is favorably related to eating habits and in which soda and fast food consumption have been negatively affected [13].

A lot has been said about the effects of advertising food directly to young adolescents using channels predominantly viewed by them, and the government has also taken required measures. However, there is limited evidence that appropriate measures are taken to improve the health of adults even though obesity and overweight are a growing concern for the country. A study by [5] et al. concluded that TV channels watched by young adolescents run food-related advertisements that mainly promote salty snacks, candies, sweetened soft drinks, and fast food joints. The median age of

15 years is the sample for this investigation. Another study found that "one in seven to one in three obese children in the USA could not be obese unless the advertisement of unhealthy food on the TV were available. The sample for this study was from 6 to 12 years of age": "High fat and high sugar meals can be considered exploitation by little children as they do not grasp that advertising items are for sale and are not capable of understanding and evaluating advertising." In the US, teens obtain insufficient daily intake of calcium. A "research revealed that 18% of youth did not consume fruit or veggies every day. Every day, 7 percent ate salty snacks and sweets, and one-third ate them many times a day. Sometimes refined cuisine is announced as a contribution to contemporary living, which typically attracts young people. Such foods frequently include large amounts of fats and sugar, which lead to excessive intake of other foodstuffs. Cooperation between households, health professionals, pedagogues, food producers, and media will assist young people in choosing educated dietary habits."

"The customer is reported to utilize nutrition labels and claims, but generally the degree of knowledge is quite poor." In a US research, the possibility of improving customer views regarding the inclusion of a variety of healthier nutrients was discovered via NCCs (Nutrient Content Claim) that "are present on less healthy food goods. At the same time, the existence of NCCs appears to diminish awareness that less healthy characteristics are present. Perceptions of product health than lead to greater intents to replace the one considered by alternative items." [8].

Existing Theories

"When information is insufficient, heuristics enable people to choose to preserve cognitive and motivational resources." Another idea is social theories that state that "to alter behavior, it is necessary to have a high degree of self-efficacy. Self-effectiveness has improved via knowledge, practical expertise and social encouragement" [12]. Central vs. peripheral routes to persuasion and the elaboration likelihood model focuses on motivation and ability of the target audience is vital criteria in objective setting. If cause and ability are both high and central processing is more likely, it makes sense to focus on changing attitudes through strong reasons why the brand is better. But if either motivation or ability is low and peripheral processing is more likely, the objective should be to create a pleasant feeling for the brand [15]. When advertisers are in high involvement situations, with the consumers seeking to solve problems or benefit rationally, the overall implication for advertisers is that advertisers should have as their aim a communication of product benefits through message contents, only that can lead to the necessary change in attitude Situations with low participation. However, this should not lead to transmission of attitude-enhanced reasons on why the brand is better than to seek increased awareness as the primary aim. Research has shown that when subjects prefer to economize on time and effort in making a brand choice, they give great weight to the fact that they are previously aware of a brand instead of probing quality differences in detail.

Methodology

The research design adopted for this study is twofold. First, exploratory research is done through a literature review. The second part is a descriptive study using the survey method will be cross-sectional, and the sample will be used, and only one questionnaire will be given to them. As a sample frame is impossible to establish, non-random purposive sampling will be done [14]. There will be a questionnaire for the sample size of 200 within the age range of 10-24. It will be designed to understand the perception of the consumers towards food that claims to be healthy.

Segregation of Food TVCs

The food advertisements on TV will be analyzed and categorized into healthy or unhealthy, based on the labels that are highlighted in the ad. Then the route of persuasion of advertisements of the products that claim to be healthy will be determined and categorized into peripheral and central depending upon the ad's message and the endorser picked to promote that product in the ad [4]. Heuristic cues will be identified in the advertisements that suggest that the product may be healthy such as 'low fat, 'organic,' 'natural,' etc. The nutrient contents will be analyzed to understand the pros and cons of the same. Products advertised will also be categorized based on the image of the parent brand [9].

Questionnaire

According to WHO, a sample of 200 youth (belonging to the age group of 10-24) will be given a questionnaire [10]. The questionnaire will be non-in-

teractive, structured, and cross-sectional. It will have two parts:

The first part will require them to fill in personal details such as name, age, height, and weight. The height and weight of the sample will help us calculate their BMI. They will also be asked whether they consider themselves health-conscious or not to establish their perceived dietary quality. They will have to score their eating habits on a scale of 1-10, where one is extremely poor, and 10 is excellent.

In the second part of the questionnaire, they will also be asked to pick up a product from each category as if they were to add it to their shopping cart. Their choices will be followed by a question requiring them to score their product choice by rating it based on the heuristic cues or labels used in advertisements of the products in that category.

The statistical tools to evaluate and interpret the questionnaire results are the chi-square test, regression, and ANOVA.

Hypotheses

With the help of a literature review, the variables to form the theoretical framework of this study were identified. The independent variables to be considered for this research are brand endorsers, labels, and perception of the brand being healthy. The dependent variable is perceived dietary quality and choice of brand.

For someone whose perceived dietary quality is good, food choices will be of high involvement, and for someone whose perceived dietary quality is poor, food choices will be of low participation while buying food items. For this research, we need to categorize the consumers to understand how advertising can influence them.

The route of persuasion taken up by an advertisement can be determined by the brand endorser so that if a celebrity endorses the product, it takes the peripheral route. If an unpopular entity supports the development, it takes the main path. Therefore the way of persuasion taken up by the brands that claim to be healthy can be determined by its brand endorser.

When they desire a shortcut to make a choice, consumers turn to heuristics. "The Heuristic representativeness is a style of thinking that perceives one unique situation as comparable to another. The heuristic availability encourages individuals to depend on accessible knowledge, even if imperfect. People depending on heuristic anchoring and adaptation prefer to build their decision based on an anchor - they refer their decisions to a starting point for adjusting their assessment. A bad factor is described as the tendency to give negative items more weight. Family heuristic, the individuals tend to have more favorable sentiments towards more everyday items, significantly influencing cognitive activity. Labels are heuristic cues that may help consumers with their buying decision. And thus, for this research, we will identify the labels or claims of the brands that determine the buying decision of the consumers".

The Halo effect makes consumers look at one product favorably if other related products have been good so far may encourage consumers to pick products from brands that they perceive to be healthy or organic, depending upon the heuristic cues that they receive will help us understand if the brand image will help form consumers' perception of healthy food or not.

- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of milk as shown in Table 1 supplement.
- Alternate Hypothesis (H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of milk supplements.
- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of cold beverages.
- Alternate Hypothesis(H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of cold beverages.
- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of hot beverages.
- Alternate Hypothesis (H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of hot beverages.
- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of dry snacks.
- Alternate Hypothesis(H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of dry snacks.
- Null Hypothesis(H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of cereals.
- Alternate Hypothesis(H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of cereals.

- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of semi-cooked meals.
- Alternate Hypothesis (H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of semi-cooked meals.
- Null Hypothesis (H_0) – Perceived Dietary Quality is independent of celebrity brand endorsers of biscuits.
- Alternate Hypothesis(H_1) – Perceived Dietary Quality is dependent on celebrity brand endorsers of biscuits.
- Null hypothesis (H_0) – Perceived dietary quality is independent of labels, as shown in Table 2.
- Alternate Hypothesis(H_1) – Perceived Dietary Quality is dependent on labels.
- Null hypothesis(H_0) – Choice of the brand is independent of the perception of the brand being healthy.
- The alternate hypothesis(H_1) – Choice of the brand depends on the brand's perception of being healthy, shown in Table 3.

Results

Findings

Table 1

ANOVA for hypothesis 3.3.1-3.3.7

Perceived dietary quality and celebrity endorsements (BG=Between Groups, WG=WithinGroups)

	Sum of Squares	df	Mean Square	F	Sig.
Milk Supplements					
BG	1.932	1	1.932	2.464	.118
WG	155.223	198	.784		
Total	157.155	199			
Cold Beverages					
BG	5.683	1	5.683	7.396	.007
WG	151.373	197	.768		
Total	157.055	198			
Hot Beverages					
BG	.150	1	.150	.189	.664
WG	157.005	198	.793		
Total	157.155	199			
Dry Snacks					
BG	3.619	1	3.619	4.667	.032
WG	153.536	198	.775		
Total	157.155	199			
Cereal					
BG	1.646	1	1.646	2.096	.149
WG	155.509	198	.785		
Total	157.155	199			
Semi Cooked Meals					
BG	.720	1	.720	.912	.341
WG	156.435	198	.790		
Total	157.155	199			
Biscuits					
BG	.231	1	.231	.292	.590
WG	156.924	198	.793		
Total	157.155	199			

Table 1 shows the ANOVA for hypotheses 3.3.1-3.3.7

Interpretation

P-value of Milk Supplements=0.118 >0.05; therefore, we fail to reject the null hypothesis implies that the Perceived Dietary Quality is independent of celebrity brand endorsers of Milk Supplements.

The P-value of cold beverages =0.007<0.05; therefore, we reject the null hypothesis, implying that Perceived Dietary Quality depends on celebrity brand endorsers of Cold Beverages.

The P-value of hot beverages=0.664 > 0.05; therefore, we fail to reject the null hypothesis that suggests that perceived dietary quality is independent of celebrity brand endorsers of Hot Beverages.

P-value of dry snacks =0.032< 0.05; therefore, we reject the null hypothesis, implying that Perceived dietary quality depends on brand endorsers of dry snacks.

P-value of cereals=0.149 > 0.05. Therefore, we fail to reject the null hypothesis that Perceived dietary quality is independent of celebrity brand endorsers of Cereals.

P-value of semi-cooked meals=0.341 >0.05; therefore, we fail to reject the null hypothesis implies that Perceived dietary quality is independent of celebrity brand endorsers of Semi-Cooked Meals.

P-value of biscuits =0.590 >0.05. Therefore, we fail to reject the null hypothesis that Perceived Dietary Quality is independent of celebrity brand endorsers of Biscuits.

Table 2

Chi-Square test for hypothesis 3.3.8

(LR= Likelihood Ratio, L by L Assn.=Linear by Linear Association, N of Valid Cases)

	Value	**df**	**Asymptotic Significance (2-sided)**
Cold Beverages * [rich in vitamins and iron]			
Pearson Chi-Square	15.616a	8	.048
LR	15.200	8	.055
L by L Assn.	.854	1	.355
VC	200		
Hot Beverages * [antioxidant]			
Pearson Chi-Square	42.448a	16	.000
LR	45.262	16	.000
L by L Assn.	3.593	1	.058
VC	200		
Hot Beverages * [better metabolism]			
Pearson Chi-Square	34.269a	16	.005
LR	39.135	16	.001
L by L Assn.	5.994	1	.014
VC	200		
Hot Beverages * [enriched with nutrients			
Pearson Chi-Square	29.331a	16	.022
LR	32.446	16	.009
L by L Assn.	10.149	1	.001
VC	200		
Dry Snacks * [baked]			
Pearson Chi-Square	64.689a	12	.000
LR	68.569	12	.000

	Value	df	Asymptotic Significance (2-sided)
L by L Assn.	12.334	1	.000
VC	200		
Dry Snacks * [complete nutrition]			
Pearson Chi-Square	35.035a	12	.000
LR	36.459	12	.000
L by L Assn.	4.074	1	.044
VC	200		
Cereal * [weight control]			
Pearson Chi-Square	34.261a	12	.001
LR	36.624	12	.000
L by L Assn.	.318	1	.573
VC	200		
Cereal * [complete nutrition]			
Pearson Chi-Square	33.406a	12	.001
LR	37.941	12	.000
L by L Assn.	.087	1	.768
VC	200		
Cereal * [rich in iron]			
Pearson Chi-Square	33.581a	12	.001
LR	35.952	12	.000
L by L Assn.	.157	1	.692
VC	200		
Semi-Cooked Meals * [whole grain with natural vegetables]			
Pearson Chi-Square	27.201a	16	.039
LR	29.529	16	.021
L by L Assn.	2.712	1	.100
VC	200		
Semi-Cooked Meals * [complete nutrition]			
Pearson Chi-Square	56.148a	16	.000
LR	68.478	16	.000
L by L Assn.	28.656	1	.000
VC	200		
Semi-Cooked Meals * [rich in protein and fiber]			
Pearson Chi-Square	50.702a	16	.000
LR	58.688	16	.000
L by L Assn.	26.912	1	.000
VC	200		
Biscuits * [rich in fiber]			
Pearson Chi-Square	41.325a	16	.000

	Value	df	Asymptotic Significance (2-sided)
LR	47.064	16	.000
L by L Assn.	11.627	1	.001
VC	200		
Biscuits * [complete nutrition]			
Pearson Chi-Square	27.994a	16	.032
LR	33.714	16	.006
L by L Assn.	9.496	1	.002
VC	200		
Biscuits * [rich in vitamins]			
Pearson Chi-Square	29.002a	16	.024
LR	30.323	16	.016
L by L Assn.	5.783	1	.016
VC	200		

Interpretations

P-value of Cold Beverages * [rich in vitamins and iron] =0.048 < 0.05; therefore, the null hypothesis is rejected implies that Buyers perceive cold beverages to be rich in vitamins and iron.

P-value of Hot Beverages * [antioxidant] <<0.05, therefore, the null hypothesis is rejected implies that Buyers perceive hot beverages to be good antioxidants.

P-value of Hot Beverages * [better metabolism] << 0.05, therefore, the null hypothesis is rejected implies that buyers perceive hot beverages to help in better metabolism.

P-value of Hot Beverages * [enriched with nutrients]=0.022<0.05. Therefore, the null hypothesis is rejected implies that Buyers perceive hot beverages to be enriched with nutrients.

A P-value of Dry Snacks * [baked]<<0.05, therefore, the null hypothesis is rejected implies that Buyers perceive dry snacks to be baked.

A P-value of Dry Snacks * [complete nutrition]<< 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive dry snacks to have complete nutrition.

A P-value of Dry Snacks * [filled with goodness]=0.033 < 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive dry snacks to be filled with goodness.

P-value of Cereal * [weight control]<< 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive cereals to be suitable for weight control.

P-value of Cereal * [complete nutrition] << 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive cereals to have complete nutrition.

P-value of Cereal * [rich in iron] << 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive cereals to be rich in iron.

The A P-value of Semi-Cooked Meals * [whole grain with natural vegetables]= 0.039< 0.05. Therefore, the null hypothesis is rejected implies that Buyers perceive semi-cooked meals to have whole grains with real vegetables.

A P-value of Semi-Cooked Meals * [complete nutrition]<<0.05, therefore, the null hypothesizes rejected implies that Buyers perceive semi-cooked meals to have complete nutrition.

A P-value of Semi-Cooked Meals * [rich in protein and fibre] << 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive semi-cooked meals to be rich in protein and fibre.

P-value of Biscuits * [rich in fibre]<<0.05, therefore, the null hypothesis is rejected implies that Buyers perceive biscuits to be rich in fibre.

P-value of Biscuits * [complete nutrition]=0.032< 0.05, therefore, the null hypothesis is rejected implies that Buyers perceive biscuits to have complete nutrition.

P-value of Biscuits * [rich in vitamins]=0.024 <0.05, therefore, the null hypothesis is rejected implies that Buyers perceive biscuits to be rich in vitamins.

Table 3

Choice of brand and perception of the brand being healthy ANOVAafor Hypothesis 3.3.9

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	43.041	7	6.149	4.492	.000[b]
	Residual	262.834	192	1.369		
	Total	305.875	199			
a. Dependent Variable: nutrient facts						
b. Predictors: (Constant), [healthyMilkSupplements], [healthyColdBeverages], [healthyHotBeverages],[healthyDrySnacks], [healthyCereals], [healthySemiCookedMeals], [healthyBiscuits]						

Interpretation

P-value << 0.05; therefore, we reject the null hypothesis implying that brand choice depends on the brand's perception is healthy.

Conclusion

As seen in columns, buyers are not influenced by celebrity endorsements when they buy milk products, hot beverages, cereals, semi-cooked meals, and biscuits. Therefore, the peripheral route of advertising will not affect them when they buy products that claim to be healthy in the categories mentioned above. Instead, they are influenced by the central route of advertising. But they are influenced by celebrity endorsements when they buy cold beverages and dry snacks, as seen in columns; therefore, the peripheral way of advertising will affect them when they buy products that claim to be healthy in the categories mentioned above.

Buyers get influenced by heuristic cues like rich in vitamin and iron when they buy cold beverages, antioxidant, better metabolism, enriched with nutrients when they buy hot beverages, baked, complete nutrition, filled with better when they purchase dry snacks, weight control, complete nutrition, rich in iron when they buy cereal, whole grain with natural vegetables, complete nutrition, rich in protein and fibre, when they purchase semi-cooked meals, rich in fibre, complete nutrition, rich in vitamins when they buy biscuits as shown in Table 2

People who claim to check nutrient facts perceive that the products that claim to be healthy are healthy implies that they might still get influenced by the health claims of the products as shown in Table 3

Further research needs to be done to understand why buyers find it difficult to choose healthy food items over junk food items.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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FMS (Federated Model as a service) for healthcare: an automated secure-framework for personalized recommendation system

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Abstract

The Healthcare sector has been emerging on the platform of data science. And data scientists are often using machine learning techniques based on historical data to create models, make predictions or recommendations. This paper aims to provide background and information for the community on the benefits and variants of Federated Learning (F.L.) with other technologies for medical applications and highlight key considerations and challenges of F.L. implementation in the digital health background. With this FMaaS, we envisage a future for digital federated health. We hope to empower and raise awareness about the environment and fog computing to provide a more secure and better-analyzing environment. The AutoML framework is used to generate and optimize machine learning models using automatic engineering tools, model selection, and hyperparameter optimization on fog nodes. Thus, making the system more reliable and secure for each individual by preserving privacy at their end devices. And this will lead to a personalized recommendation system for each individual associated with this framework by deploying the Model to their devices for on-device inferences through the concept of differential private Model averaging. With this framework, users don't have to compromise with privacy, and all their sensitive data will be secure on their end devices.

Keywords

FMaaS, AutoML, Federated learning, Healthcare, Digital Health, Privacy-preserving, Model averaging

Imprint

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Introduction

Due to the deployment of deep learning-based Machine Learning models in digital healthcare, radiography, pathology, genomics, and many other disciplines have made significant advancements. Medical datasets are used to train and test modern Deep Learning models, which include many parameters to capture the complexity of these applications [1]. A significant number of firms with curated data are required to produce clinically accurate, reliable, and fair models while also generalizing effectively to unknown data [2]. Suppose you want to train an automated heart attack detector using an extensive annotated database [3]. This kind of evidence is difficult to collect and maintain. Because health data is highly private and subject to monitoring, it cannot be utilized for research without the patient's permission and ethical approval [4]. When it comes to evading such restrictions, data anonymization is frequently recommended. Still, now we know that deleting information such as the patient's name or date of birth is not always adequate. It's also because medical data are both susceptible and expensive to obtain [5]. Federated learning is a machine learning program that aims to train a high-quality centralized model. At the same time, training data is spread to many customers with incoherent and relatively slow connections to each network. We consider learning algorithms for this context where every client calculates the current model updates individually depending on their local data in each turn and communicates this update to a central repository where the client-side changes are aggregated to determine a new global model [6]. Federated Learning (F.L.) is a software model designed to tackle data governance and privacy issues by collective algorithm training without sharing the underlying datasets. The technique was initially built in a particular context but has increasingly gained popularity for healthcare applications. It solves the issues that currently occur when attempting to integrate medical data [7]. It implies that F.L. enables organizations to exchange views, such as in a global or consensus model, without revealing patient data.

Because critical training data cannot be transferred outside the companies' firewalls in which they reside [8], F.L. has a distinct advantage. Each participating company performs its Machine Learning (ML) process, and only model characteristics (such as parameters and gradients) are shared between them. The informed consensus model benefits from the information collected across all institutions [9] once the training is completed. A successful F.L. implementation has the potential to provide precision medicine on a broad scale, and we think that this is the case. This would promote models that make objective judgments, ideally reflect a person's physiology and react to uncommon illnesses in a way that respects concerns of governance and privacy, especially in pandemic situations like COVID-19 [10].

The recent rapid growth of medical computerization and subsequent developments in clinical science's automated data processing produce large amounts of data from healthcare. The proper usage of these large data is directly linked to the success of the health sector as a whole which is of tremendous concern regarding medications, medical treatment which public safety [11]. Accordingly, regulatory frameworks or privacy protections have been established to limit access to data. The Protections for the Protection of Personally Identifiable Health Records, commonly known as the HIPAA (Health Insurance Portability and Transparency Act) Protection Rule2, sets the first national requirements for protecting confidential or secure health records (PHI) for patients in the United States. On 25 May 2018, the European Union's General Data Protection Regulation (GDPR) established strict data security and privacy rules, highlighting the need for an open and transparent collection of user data [12]. The balance between processing medical data and preserving patients' privacy has also become an important and challenging problem. Federated learning, an approach for developing a shared global model with a central repository while maintaining all confidential data in local entities where the data belongs, is yet another effort to connect the scattered sources of health care data while losing data privacy [13].

And to simplify and render modeling more compatible with the data type of data collected from wearable devices and other end devices and more reliable and efficient, we use the concept of AutoML to render our approach more manageable in terms of reiterating the Model to find the best prediction. AutoML refers to systems that, in every phase of the data sciences, automatically pick and optimize the Model of machine learning [14]. The function creation process is stressful for data scientists, so several solutions have been suggested to create new parameters dynamically and choose the best subset of parameters while maintaining the high-performance model [15].

Conceptual Model and Related work

It is a machine learning standard to centralise the training data on a single computer or in a data centre. Also, Google has built a cloud infrastructure that is one of the biggest and most reliable, which allows us to analyse the data and improve our services.

While retaining all of the system's training data, federated learning allows mobile phones to learn a particular prediction model without having to save cloud data [16]. In this, the current Model is downloaded from your computer, enhanced by learning from your phone's data, and then summarized as a tiny centered change update. Using encrypted communication, this model update is sent to the cloud only, where it is automatically pooled to enhance the shared Model along with other user changes [17]. All training data is left on your computer, and there are no individual updates in the cloud.

On Android, Federated learning uses the on-device history to propose improvements to the suggested question model for the next version of Gboard. This system requires sophisticated stacking technology to extend to millions of heterogeneous Gboard-running phones [17]. The system will then need to communicate and aggregate updates of the Model in a manner that is stable, efficient, scalable, and tolerant to faults which is shown in Figure 1.

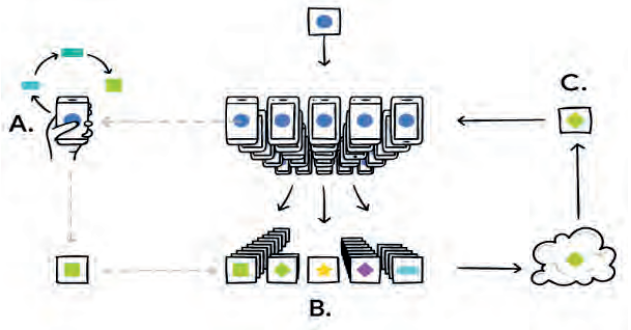

Figure 1. The Model is customized locally by your computer, based on your use (A). Multiple user modifications are aggregated (B) to create a consensus adaptation (C) to the common norm, after which the cycle is repeated.

Literature Review

Researchers at CSCW have also explored the collaborative factor of data science work. They have performed ethnography research to discuss cooperation on a hackathon of civic data, where computer science professionals are helping non-profit organizations obtain knowledge from their results have also consulted data scientists and informatics experts working on similar data science projects[18]. Their findings reflect part of the preceding literature in the data science workflow with multiple steps examined current literature on the usage of machine learning technology by data scientists, from which they offered recommendations for the future design of AutoML systems [19].

Using the inexpensive computation usable on network edges, the F.L. approach also helps us increase learning. A local training dataset on each individual's device never gets submitted to the server [20]. Additionally, every individual measures the new global Model that the central server retains and then communicates the update. The main insight is that while we optimize nonconvex loss functions, an average of parameters over many updates on clients yields surprisingly good results [21].

Federated learning is a method to train with a central server on a standard global model while retaining all sensitive data in local institutions. Their survey focuses on evaluating recent trends in federated learning, including, though not limited to, health informatics [22]. They aim to have a valuable tool for information health technology and computer work on current developments.

Huawei Technologies Researchers have been working on algorithms to federate the standard collaborative filter using an approach based on stochastic gradient descent. By incorporating an adaptive learning rate, their Model achieves robust and stable solutions. And results show that the federated Model can provide recommendations of similar quality. They considered this work as a first step towards a federated model of privacy-conserving recommendation systems. They aimed at exploring multiple directions in the future in this research line.

An important field of research in computer science is automated machine learning. It tends to support non-experts to implement off-the-shelf machine learning. While some AutoML use cases have already been found in the healthcare field, further research is needed. This survey will serve as a simple guide for health researchers who want to apply data analysis techniques to their field of interest.

Edge Network Computing Privacy-Preserving Asynchronous Federated Learning System (PAFLM) for resolving the functional needs of multiparty data learning without disclosing personal information. PALM offers more flexibility and privacy to the learners without losing the training accuracy. The research nodes add the gradient to the server parameter is satisfied. All nodes execute the above measures asynchronously without the remaining nodes waiting for or synchronizing the learning process. The nodes interact with the parameter server only during the federated learning cycle, having obtained no knowledge of the other nodes beyond the global parameters which are retained jointly.

Methodology & Experimentation

To make this federated approach feasible, we had to overcome numerous computational and technological challenges. XGBoost (XGB), a gradient-boosting method, is the most successful of the algorithms we have used to address healthcare issues. An optimization method such as XGB operates on cloud servers over an enormous, homogeneously partitioned dataset in a conventional machine learning software. High-throughput connections to the training data with minimal latency are required for these highly iterative algorithms. Thus, we are designing this framework on fog computing, which brings the cloud closer to its users. Therefore, it enables data collection and local processing decreases network latency and bandwidth utilization. Fog computation speeds up knowledge and reaction to incidents by removing a round trip for research into the cloud. It also preserves critical IoT data by analyzes inside company walls.

Data is dispersed unequally among millions of computers in the Federated Learning system, on the other hand. They are considerably more latent, with lower-speed connections and can only be fitted on a temporary basis. The FedAvg Algorithm, which can train deep networks with 10-100x less transmission than an open federated XGB version, was developed to overcome these bandwidth and latency constraints. However, it is also necessary to calculate higher-quality improvements than flat gradient measurements using the powerful processors in modern end devices. Since iterations require less to generate an efficient

model for high-quality notifications, testing may utilize even less communication.

Federated Learning Concept

The optimal problems also have the following properties:

- Learning on wearable system real-world data offers a clear benefit overtraining of the widely used proxy data in the data center.
- This data is vulnerable to privacy or is huge (as opposed to the size of the Model), so it is better not to log it solely for model training purposes in a data center (serving the oriented collection principle).
- Data labels can be extracted from the user's knowledge of controlled activities with his computer. Most models that power smart behavior on mobile devices follow the requirements set out above.

Privacy for federated learning

The two major aspects of data privacy of Federated learning are:

Initially, it is important to understand what a threat may know by taking a look at the common characteristics of the Model that is used in the optimization process. A more specific defensive strategy must be developed in lieu of this open-ended defence system. Much yet, because the Model depends on a large number of users sending alerts, the majority of application groups find such assaults even more difficult. While such methods are great for protecting real, privacy-sensitive learning tasks, even when the opponent knows subjective side information, they nevertheless come at some cost in terms of effectiveness, since they introduce some random noise to the training model.

The next question is what an attacker can know by having access to an individual client's update messages. If one trusts the central server, then the primary lines of defense for this type of attack are encryption and other standard security protocols. *Implementing local differential privacy* may provide greater assurance where we noise the individual changes, instead of making a final model less clear, this noise obscures the fact that the fog server is unable to make any conclusions about a client. It is also feasible to aggregate several client alarms via strong multi-party computation, allowing for local differential privacy with much less random noise. Even holding an "anonymized" dataset can still jeopardize user privacy by joining other data. The information sent for F.L., by contrast, is the optimal update required to improve a given model. The warnings may (and should) be ephemeral in themselves. Federated learning is therefore superior to logging raw data directly into a central server on fog nodes and can be further improved with proven techniques to give even greater guarantees of privacy, such as homomorphic encryption.

Federated Optimization

FL believes that optimisation is a problem that might be solved with the aid of federated optimization, or distributed optimization. The distinctive characteristics of federated optimization are the same as those of the traditional issue of distributed optimization:

- Non-IID: Training data for a specific customer usually focuses on a limited user's usage of the mobile device, and thus the local consumer dataset might not be reflective of population distribution
- Unbalanced: Likewise, some customers may use the service or device that produces training data much more intensively, This results in some customers having extensive training data for local conditions, while others have very little or none at all.
- Massively distributed: For this study, we'll concentrate on the Non-IID and Unbalanced Properties, which describe some key developments in algorithm growth. Federated optimization platforms, which are implemented, have many practical challenges. If you keep your customer data up to date, you'll be able to react more quickly to changes and will have customers who provide their information accurately.

The FedAvg Algorithm

As the optimization algorithm, the recent multitude of effective deep learning applications depended almost entirely on variants of XGB; indeed, many developments can be understood to be better suited to optimization by simple gradient-based methods by adopting the Model's structure (and thus the loss function). This approach is computationally effective but needs much training to produce good models.

In communication rounds, we believe that there is an asynchronous communication scheme going. There is a fixed client array, each with a fixed local dataset. A fraction of random clients is chosen at the beginning of each round, and the current global algorithm sends by the server (e.g., current model parameters) to each of those clients. Then the client runs local

computations on the basis of a global state and local dataset and sends the server an update; then the server makes some changes to its global condition, and the loop repeats those changes.

Figure 2 shows the proposed FMaaS framework implemented in fog node with homomorphic encryption used for secure aggregation of models. In this, A parameter server then receives the Model and distributes it to all the nodes. Each node then trains a local model several times. Afterward, the updated models are sent to the parameter server for aggregation. After the Model is agreed upon, it will be shared for future use.

Federated Learning implemented on fog node of fog computing through AutoML. (i) On-device data gets collected from 'n' number of distributed end-devices and distributed aggregation sent to fog server after getting calculated. (ii) AutoML process performed on fog server and gets a threshold value which will further compared with on-device data through Aggregated Operator on distributed devices. (iii) Federated Aggregation will then be sent back to the server after combining reports from multiple devices (then sends ephemeral reports i.e. never persist per-device reports) (iv) The process gets repeated several times as many devices may not be available for every round. (v) Secure-aggregation performed between on-device and server to compute a vector sum of encrypted device reports with the help of homomorphic encryption. (vi) Finally, the updated Model on the fog server will be deployed to devices for on-device inference after model validation. And thus, through this framework, doctors, guardians, etc., get insights from the data and can monitor the health remotely and can have a keen eye to have a regular investigation.

AutoML for optimizing recommendation system process

To make our recommendation system more accurate and flexible, we have performed the AutoML concept on AzureML platform.

To do this, you may supply a data table and choose the target column to forecast, such as a number (for example, heart rate) or a category (like spam or not spam). The Azure AutoML service will use a set of algorithms to run many simulations and arrive at the optimal Model. Once you have done that, you may publish the Model to Azure Gallery, or use Azure ML Studio to refine it further.

Data Preprocessing and Feature Engineering

In particular, this function involves the identification of data form and schema which was not com-

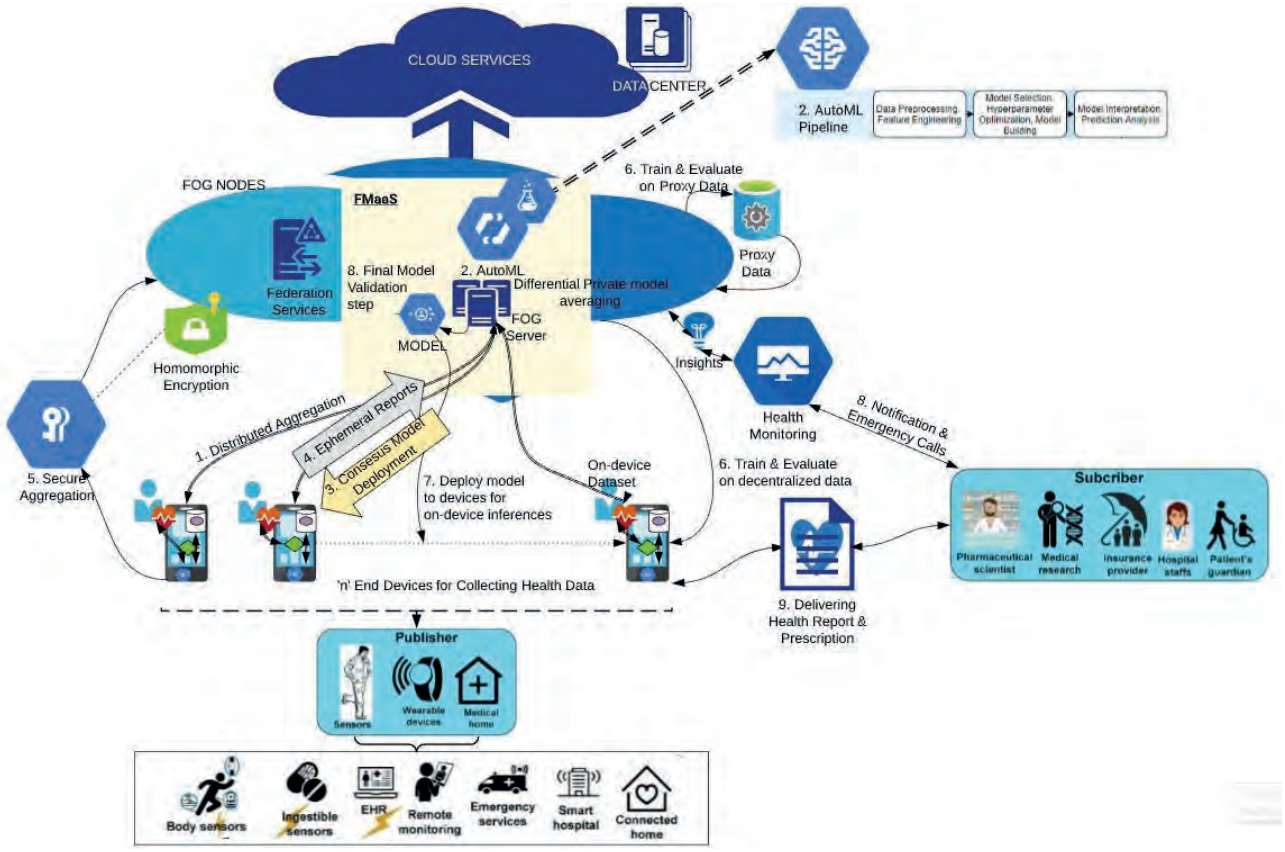

Figure 2. Proposed FMaaS framework

monly supported by AutoML tools. Nonetheless, the tools have the appropriate function development for the next step of the process until data types are defined. AzureML appears to be further ahead in this regard by allowing the identification of different unique data types (e.g., names, addresses, telephone numbers, etc.).

Model Selection, Hyperparameter Optimization, and Architecture Search

During the first stage, the extracted features are then used to train a few different brand models, each with several parameter sets to enable optimal Model (or model group), and the last one method is used to support a collection of existing ML algorithms designed to create a network. The optimal Model (or model ensemble) is selected. The parameter space is typically trimmed to reduce the time required for model search and optimization of hyperparameters. It's possible to get better results by using Auto-sklearn through python SDK. A preprocessed'meta-function' from previously trained datasets is used in Auto-Sklearn. Their first Model is built using the meta-learners from the target data set using themetafunction given to the target data set. Model selection and hyperparameter tuning are explored in the second method.

Model Interpretation and Prediction Analysis

In this section, we provide a comprehensive representation of outcomes through model dashboards, function sense, and various methods of visualization, such as lifting maps and distribution of predictions. However, AzureML states obsolete data points that the best Model has not been optimistic regarding predictions and supports trigger code, partial dependence, etc.

Analysis of work done

After proposing FMaaS framework, and AutoML concepts to make a more reliable and flexible model in healthcare, Our team came up with the following criteria to safeguard sensitive data. As a result, trade-offs, tactics, and lingering dangers relating to F.L.'s privacy-preserving capability should be considered.

Privacy Vs. Performance. Although FL's primary aim is to preserve privacy by sharing model updates rather than data, it does not address all privacy problems, and in general, similar to ML algorithms, there will still be certain dangers associated with using F.L. F.L.'s privacy-preserving methods provide security levels that surpass the existing commercially available ML models today, according to the researchers.

Level of Trust. There are two kinds of F.L. cooperation that may be entered into by the parties involved:

If both parties are considered to be trustworthy and bound by a mutually enforced agreement, we can eliminate many of the more nefarious motivations, such as systematic efforts to acquire private information or intentionally alter the Model. There is no longer a need to use complex countermeasures since the concepts of collaboration are being used.

For systems that function on a wider scale yet lack trust, it is impossible to create a legally binding agreement that ensures all participants are behaving ethically. These risks will be mitigated by using security methods, such as encryption of model submissions, secure authentication of all participants, traceability of activities, differential privacy and verification systems.

Information leakage. F.L. systems, by definition, do not require the exchange of healthcare data across institutions. It's also important to note that the shared knowledge reveals implicitly private data utilised for local training, such as the inversion of model modifications or adversarial assaults. Reverse engineering leakage rises as a consequence if adversaries can identify model changes over time or witness various model updates (e.g., cause additional memorization by others via gradient-ascension style attack). Research on countermeasures to guarantee differential privacy is essential and ongoing, such as reducing the granularity of the shared model updates or introducing variable noise.

Data heterogeneity. It's important to note that medical data may be very varied due to factors such as collection procedure, medical equipment brand, and area demographics. Many existing F.L. methods and tactics assume that the data is independent and identically distributed (IID) among the participants. While not all institutions have access to the same information, initial results indicate that F.L. training on non-IID medical data is possible. When this happens, however, methods such as FedAvg usually fail, defeating the entire purpose of collaborative learning strategies.

Traceability and accountability. The repeatability of a system in healthcare is essential to F.L., just as it is with other safety-critical applications. In order to guarantee that device actions, data access history, and changes in training configuration, such as hyperparameter tuning, can be observed throughout training operations, the traceability criteria must be fulfilled In addition to recording a model's training history,

traceability may be utilised to prevent overlapping the training and test data sets. Flare-induced blindness (F.L.) prevents researchers from examining images of the models they are training on. Federations may opt to offer some sort of secure intra-node viewing facility to satisfy this requirement, or maybe even some utility to explain and understand the global Model, despite the fact that each site will have access to raw data.

Results & Discussions

Federated learning distributes to the edge the method of machine learning. It helps mobile phones to collaboratively study a common pattern, to use the training data of the device, and to retain the device data. The findings are as follows; we have obtained from the above analysis:

1. ***Increasing computation per client***, where each client calculates for each contact point more complicatedly, instead of simply calculating the gradient.

2. ***Increasing parallelism***, where we have more customers, we work at every communication round separately. To calculate the number of communication rounds, for each parameter setting combination, we create a learning curve, cause the curve to develop monotonously, and then determine the number of rounds between the various curve points at which the curve approaches the target using linear interpolation.

3. ***Differential privacy***, statistical analysis of common patterns of learning in a dataset without memorizing individual examples. This uses noise to mask an individual's impact on the learned Model (don't memorize individuals' data). Differential privacy techniques can provide strict, worst-case privacy guarantees for actual, privacy-sensitive learning tasks, even when the opponent has arbitrary side information.

4. ***Robustness and attacks***, TensorFlow Federated (TFF) can be used to simulate the considered targeted attacks on federated learning systems and defenses related to differential privacy.

This is achieved through the creation of an iterative process along with potentially malicious clients.

- You can implement novel attacking algorithms by writing a client update function which is a Tensorflow function.
- By tailoring 'tff.utils.StatefulAggregateFn' which aggregates client outputs to obtain a global update, new defenses can be implemented.

5. ***Personalization*** is an important field of research in a federated learning environment. Customization aims to give different users different models of inference.

One solution is to allow each customer to tailor their local data to a single global model (trained using federated learning). That approach has links with meta-learning. You can explore and compare different strategies for finer tuning:

- Use the local data sets of each client to implement a tf.function starting from the initial Model, train, and test a custom model.
- Specifies an OrderedDict which maps the names of the technique to the respective tf.functions and creates a TFF computation to test them.

By developing and deploying FMaaS, those who will be benefitted are:

Clinicians will be able to supplement their own expertise with expert information from other organisations by utilising ML-based systems, providing a continuity in diagnosis that is not currently possible.. These promises apply to any machine learning system, but systems trained by the federal government should potentially provide fewer biased judgments and be more sensitive to extreme instances, such as the COVID-19 pandemic, since they will have seen a more complete view of the data distribution.

It's common for people to seek medical care at their local hospitals and doctors' offices. By implementing F.L. on a worldwide scale, clinical choices will be more accurate, no matter what area they are made in. The same high-quality ML-assisted therapy may be accessible to patients in distant locations, such as COVID-19.

Health care facilities that can prove the source of patient information will retain complete control and ownership of patient records. In this way, they are able to minimise the danger of misappropriation while dealing with other parties. It would also be necessary to invest in on-site computer capabilities or provide private cloud services in order to participate in federated efforts.

Since the integration of learning from multiple devices and apps may enable the ongoing development of ML-based systems without disclosing anything patient particular, manufacturers of healthcare software and hardware might also profit from federated initiatives and infrastructures for F.L.

Conclusions

A new model creation framework for Artificial Intelligence (A.I.), Federated Learning, will increase in

popularity and acceptance since it is dispersed over millions of mobile devices, offers highly customizable models, and doesn't violate user privacy. It allows for better models, reduced latency, and less resource use while preserving privacy. And this method has another immediate benefit: you can automatically use the updated Model on your computer, in addition to upgrading the existing Model, enabling customized experiences by using your wearable devices and handsets.

F.L. promises to tackle the challenges of privacy and governance simply by letting algorithms learn from non-co-located data. F.L.'s ability is, therefore, to provide managed, indirect access to broad and extensive datasets that are required to build ML algorithms while maintaining patient privacy and data management. Notably, this includes both the training and validation phases of development. Through the use of large-scale validation directly in institutions around the world, F.L. could open up new research opportunities, such as for rare diseases like COVID-19 where incident rates are abruptly exponential and a single institution is unlikely to have a large enough data set to apply ML techniques. The fact that other F.L. participants never get direct access to other entities' data and only get the model parameters aggregated over many participants ensures a certain level of anonymity. A client-server design in which the aggregation and dissemination are handled by a federated server also allows for the anonymity of the participating parties. Succeeding implementation of F.L. would represent a paradigm shift from central data centres or reservoirs, with significant implications for the different stakeholders in health care. This architecture improves user trust and understanding, and model metrics and visualisations are the most valuable information that data scientists can provide to physicians to evaluate their patient's daily health report. This framework can be very effective in case of unavoidable situations or pandemics like COVID-19 and a secure one to preserve patient's privacy at the end.

Limitations

FL relies heavily on standardization and homogenization in data format for seamless training and predictive model evaluation. It includes significant efforts to standardize managers of the data.

For society or the economy, such a centralised approach is not ideal, since it may lead to the monopolisation of just a few powerful players over time A lack of interoperability and interpretability of A.I. systems-driven choices would eventually prevent smaller or even larger businesses from participating in A.I. innovation, as well.

Recommendations and Future Work

The followings are the recommendation for the healthcare sector in achieving a more secure and efficient model as there are also some concerns regarding privacy, trust, and security in FL:

- This framework can also be implemented on decentralized architecture on a peer-to-peer design. In this, each node transmits its locally trained Model to any or all of its peers and each node aggregates it.
- Implementing the blockchain concept will help healthcare organizations bypass conventional databases and make it easier to exchange confidential medical data safely. Blockchain technology not only increases transparency between patients and doctors but also ensures effective collaboration between various healthcare providers and research organizations as it works on decentralized architecture on a peer-to-peer design.
- As DataRobot, H2O-DriverlessAI, Auto-sklearn, and Darwin provides you with more functionality for supervised methods, you can use them, which also offers additional unsupervised methods such as clustering and identification of outliers. But AzureML is the best platform for on-cloud modeling.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Effectiveness of blockchain to solve the interoperability challenges in healthcare

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Abstract

This study aims to explore the potential of Blockchain to transform healthcare, build the patient-driven healthcare ecosystem rather than the current institutional driven and enhance the privacy, security, and interoperability of healthcare data and check the counterfeit drugs. Interview excerpts from Industry experts/developers in the field of IT and experience from the implementation of the technology in the financial world will help understand its viability in healthcare. Consulting with domain experts is a qualitative process that involves comprehending the perception of the experts. The research paper will help the healthcare sector lay down future business strategies to redefine its businesses by overcoming the increasing threat on patients' private data and resolving complex supply chain issues. A decentralized ledger can prevent massive revenue loss due to counterfeit drugs to track and verify each drug's movement on the unchangeable record. The primary and secondary research is original, adding its authenticity with interview excerpts of domain experts. The results of this research paper will help identify the transparency, immutability, cost-saving, and streamlining of business to be brought by Blockchain in health care. It would be the transformational journey from innovation to market the quality products to the end consumer.

Keywords

Decentralized ledger, Transparency, Immutability, Electronic Healthcare Records, Blockchain, Ecosystem

Imprint

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Introduction

Rapid changes in technology have not left any economic sector untouched, and so is healthcare. Rapidly changing regulations, [1] technology developments, and patient expectations created a new opportunity to turn around medical practices to develop a patient-centered system. The Healthcare system is evolving itself in a big way to enhance patients' experience by adopting technology to store, process patient's data and turning the system to patient-centric. But rising cyber threats and quench to access data by unauthorized sources are also posing a challenge to healthcare providers and patients. [2] Also, it is causing psychological stress to the already suffering patients, challenging established regulations, causing an unsecure environment for the healthcare providers resulting in the wastage of time and resources to secure healthcare data by the already heavy burdened healthcare sector. Rampant drug counterfeiting has also resulted in an increase in fake drug markets across the globe, which has threatened people's life. The development of Blockchain technology has tried to address these challenges.

Literature review

This research paper is based on the use of Blockchain technology to provide a secure environment and unlock barriers to data-sharing, which help industry-wide shift to value-based care. Blockchain technology is expected to address supply chain issues by checking drug counterfeiting, healthcare data security concerns and develop a robust drug recall management system.

The workflow of a Blockchain-based healthcare system. The Blockchain system consists of four layers: raw healthcare data, blockchain technology, healthcare application, and stakeholders. [3] The ***first*** layer includes clinical data, lab data, claims(insurance), social media content, cost incurred in additional research and other activities, medical images generated, and patient-generated data. The foremost task of every exercise is to collect the data and securely store it. The ***second*** layer refers to the decision how and where to use blockchain technology, i.e., decide the different parameters of use like the type of Blockchain to be used, networks and protocols decision to share the data over the network ensuring the safest proto-

col to use, components and services to be rendered, and blockchain platforms. [4] The ***third*** layer is developing blockchain-based applications and using them in supply chain management, data management, and the implementation of the internet of medical things. The ***fourth*** layer includes the stakeholders of the application like government, public, blockchain users, researchers, clinical trials, patients, researchers, etc.

Current Trends and Developments

Blockchain being the decentralized ledger uses algorithms and strong encryption to record digital transactions in a transparent and immutable way can provide a reliable solution to the existing challenges. An IT enterprise in the US created a product to help the healthcare industry securely store digital records on the company's blockchain platform accessible by hospitals and healthcare administrators. Currently, physical documents are subject to manipulation, loss to accidents, unsecured environments vulnerable to hackers. [5] Data sharing is also one of the significant challenges. It may be regarding sharing patient data among various stakeholders to access the patient's historical data and in the supply chain to check counterfeit drugs. India is the largest exporter of drugs shares around 35% of the world's counterfeit drugs. India uses serialization techniques to overcome this challenge but can still identify the source of counterfeiting in specific geographies. With its nature of shared records of transactions, Blockchain has become a new hope to overcome existing challenges. [6] Every year medical industry lost a staggering 11 billion dollars due to misinformation. Delayed access to patients' medical records exhausts staff resources and causes delays to patient care. Drug trafficking also causes considerable losses to companies' revenue. In 2017 a US company developed a sharable network of Blockchain to enhance the reliability, integrity, and efficiency of the medical supply chain. It helps to scan and verify all points of the supply chain and weeds out around 15% of all fake medicines in the world.

A gap in Existing Research

The research work done till now in the field of Blockchain lacks scalability. All products developed have been used at a tiny scale. [7] The scalability issue in this research paper has been tried to address using cloud storage, big data, and machine learning. This is the only solution available to store and manage extensive scale data, say for a country, and the use of machine learning & Big data to process this large amount of data can be worthwhile.

Research methodology

Blockchain technology is still in the pre-mature stage, which companies and regulators are still to be accepted globally. Interview excerpts in the form of a research paper published have been referred. [8] Many governments/regulators across the world are still suspicious of what results from technology would bring. Some governments have started on a trial basis to test technology with restrictions like keep it centralized monitored, which is against the very nature of technology that involves decentralization. Therefore, very little knowledge among the masses about Blockchain technology. Hence, experts' views, the experience of companies that developed products using this technology, and companies that implemented are considered to discuss it.

A white paper published showed the potential of blockchain technology to eliminate the friction and cost of current intermediaries, which can be passed on the patient and hence, reducing the overall cost of the treatment. Blockchain has the potential as an enabler for nationwide interoperability. Health information exchange in a secured environment is one of the crucial problems the pharma sector faces worldwide.

Data Availability

Blockchain developers collaborated with healthcare providers of different areas like hospitals, drug manufacturers, regulators, etc., to collect data and develop respective products. For example, one of the research cases involves the FDA (the world's most reputed drug regulator) piloted blockchain-backed project. It measures effectiveness based on the tracing of prescription drugs and vaccines. Today, [9] worldwide, drug counterfeiting has emerged as the major problem due to the complex supply chain system, which poses a danger to patient health and drug manufacture reliability. One aspect of this project is also connecting the existing serialization technique with the blockchain technology for the effective tracing of drug counterfeit from the plant manufactured to the end customer delivery. [10] Another one is, today notifying members of the supply chain takes about three days, but with the use of Blockchain, it will be reduced to just a few seconds. Digital ledger records shared, unchangeable peer-to-peer transactions by linking blocks carry information

of the previous block in the form of hashed code. Reliable cryptographic techniques used in the Blockchain allow participants in a network to exchange, store, and view information even if they are connecting for the first time. [11] A significant challenge of Big Data technology, centralized and opaque, has been somewhat overcome by Blockchain by its decentralized nature and transparency in sharing information. Interaction with Blockchain is known to every participant in the network and registering an unchangeable audit trail of all transactions. This exercise aims to establish pan nation interoperations using safe, omnipresent network infrastructure, demonstrated recognition and validation of all participants, and steady presentation of confirmation to accessible pharma details.

Recall Management System

Over the years, national drug regulators and other agencies' drug recall data will be used to develop a transparent and decentralized drug recall management system based on blockchain technology. [12] By providing a single shared source of reliability among healthcare partners and allowing patients access to electronic healthcare records, clinical notes will improve patient's safety in case of a product recall. This will enhance practical learning and experience with interoperability among existing healthcare trading partners, establish a deeper understanding of the required process-level interactions over stakeholders, and identify opportunities to develop solutions to improve healthcare supply chain security. [13] Immutability of data allows the use of this technology. It is considered in the highly regularised healthcare industry, which enables real-time reconciliation of all transactions without seeing the underlying data. This can reduce costs, eliminate manual processes and automate, and introduce a transparent supply chain among trading partners. [14] This report would contain critical findings of the opportunity, challenges, experience of specific organizations which implemented blockchain technology, benefits over existing practices, and the efficiency technology to being transparent. Also, the most crucial part is the cost-effectiveness of the technology to implement and cost-saving. The next major challenge is scalability which will be addressed using Cloud storage, Big Data technology, and Machine Learning. When Blockchain-based products are used at the national/global level, there would be a humongous amount of data to store and process.

Data Storage

Cloud storage is the one option to store a large amount of data. It will address data-sharing, global access to data, data management, and availability of data all the time.[15] A considerable amount of money spent on data storage and management can be saved. Hence, it will help to lower healthcare services costs and maintain transparency in sharing and availability of data all the time.

Data Processing

Big data to be used for processing such a large amount of data. Along with data processing, machine learning will be used to build models that can make predictions on future data and help healthcare providers take timely actions and save people's lives. [16] Interaction with Blockchain is known to every participant in the network and registering an unchangeable audit trail of all transactions. Each transaction in the Blockchain is recorded as a data block containing a hash, timestamped of recent transactions and the previous transaction. In this way, all the data blocks are arranged in chronological order, and those connected blocks are called Blockchain. So, if one block is modified in the chain, all the blocks after the modified one must be changed simultaneously, making it practically impossible to alter any obstruction in the middle. Hence, the blockchain data network is immutable. It is expected that insurance claim and medical record management, biomedical research, clinical trials, future data of health and biomedical ledger will be improved with the adoption of the technology and critical aspects like decentralized management, robustness, data origin, unchangeable audit trail, and improved safety and isolation of data. One best feature is an innovation that seems to be achieved with Blockchain to retrieve concerned data. It is believed that sharing, operating, and utilizing medical data by data subjects besidesthehospitals. The basic notion of establishing a patient-centered interoperation approach is different from the existing institution-driven interoperation. But it comes with data security, privacy, challenges of technology like volume, velocity, stimulus, and transparency.

Results and analysis

The results of some blockchain-based products and their ability to track and trace the complex supply chain process have been encouraging. Projects fo-

cused on the applicability of technology and identifying challenges associated with interoperability among stakeholders.

Implementation

Using serialization(currently) to track the supply chain involves applying unique identifiers to a healthcare product. This serialization code is the unique code of serial numbers printed and required to be applied to all supply chain baggage. But today, it is known to the manufactured party only. In the future, it is aligned so that it can be shared with all the members of the supply chain, and it should be an electronic, printable number. Each transaction in the Blockchain is recorded as a data block containing a hash, timestamped of recent transactions and the previous transaction. Hence, the blockchain data network is immutable. It would be difficult for drug traffickers to tamper with the electronic code. Across the globe, around 200 billion dollars of amount has been estimated, originated out of counterfeit drugs. India is the largest exporter of medicines globally and constitutes a significant contribution to counterfeit drugs, which is due to the existing complex supply chain system. Hence, it is required to enable interoperability in an immutable, distributed ledger between supply chain partners.

Drug Provenance and Data Privacy

Tests by some companies are accurately captured on the Blockchain by recording shipment, receiving, and dispensing actions against electronically recorded product data to create a link of product movement. Data privacy was maintained among all partners through permission view. Regarding patient safety, all product alerts for investigation and recalls can quickly be sent and received among network partners who have previously possessed the impacted product. Network partners can soon identify products subject to an alert that are or have been in their possession through the unique product identity of the solution. Blockchain enhanced the functionality to accelerate the communication process related to alerting downstream members with an affected inventory. The current recall process is costly and time-consuming due to a lack of standardized methods and alert mechanisms between trading partners. Currently, it takes up to 3 days to identify impacted products and conservative downstream partners due to the lack of interoperability and visibility to lot-level information. With the use of blockchain technology, the process can be exponentially expedited. All trading partners can be alerted in as little as ten seconds. Blockchain technology-based product developed by Boston-based healthcare company to automatically accommodate patient care actions, managerial actions, and enhance outcomes. It tests technology while aggregating patient information into a disseminated ledger that connects all the stakeholders, including public healthcare authorities, in an ever-fasting way. Data and treatment accuracy are ensured by implementing intelligent contracts between end-to-end stakeholders. Another Atlanta-based healthcare firm successfully authorizes healthcare stakeholders to acquire, save, and move all necessary data through Blockchain in a secured environment faster than ever. Another critical issue regarding supply chain management, also shown promising results in overcoming challenges.

Supply Chain Solution

Block pharma, a healthcare supply chain company, developed a solution to track and trace drug counterfeiting. An app-based tracking system was designed to track and validate all shipments points by letting patients know through the app if they are consuming any counterfeited medicines. The blockchain technology-based supply chain management system has helped weed out almost 15% of all counterfeited drugs. Tierion created a blockchain-based product to validate reports, details, and medicines to store clean historical data. For this, timestamps and identity were used to keep evidence of possession throughout a drug supply chain. It also suggested developing a network coin to make the bitcoin more versatile. Seeing the positive and promising results of various companies' test projects or blockchain-based products to overcome the interoperability and supply chain challenges, the Centers for Disease Control (CDC), US federal government agency shown interest in blockchain technology. The application of digital recorded time, stakeholder-to-stakeholder health recording, and sharing information capabilities can help detail illness outbursts in real-time.

The provenance of the illness outburst can be traced by studying the trail of reported outbreaks and can be helpful to defeat the disease. Now, a surveillance system based on blockchain technology is being developed by IBM in collaboration with the CDC to help in collecting patient and prescriptions data effectively. The field of

genomics can also be advanced using blockchain-based technology. Genomics can bring enhancements in future generations to weed out congenital disabilities by altering DNA features and making them financially viable. Around two decades ago, it cost around a billion-dollar which has come down to a thousand dollars. To unlock the origins of human history past to millions of homes, companies are bringing DNA tests. Blockchain features and the capability to securely store and process data to house billions of genetic data points can be the perfect fit for this growing industry. It will make it possible to allow people to sell their encrypted genetic information to create a database based on genetic information, which will give scientists access to insightful information most quickly. A huge sum of money is spent by companies on third party connections to collect genetic information. Sharable ledger has been used by one Boston based company and finds its capability to stop unnecessary spending and remove middlemen in the research process. It is found helpful in eliminating middlemen and incentivizing users to securely sell their encrypted genetic data by creating a genetics database. It uses a blockchain-backed platform to ease the search, store, buy, and sell of genetic data. It uses a unique token issued to each user to access the genetic database based on reliability to study the genetic information and advance the research. It is also augmenting its platform to allow the user to voluntarily sharing their genetic data by building it more trustworthy. Stakeholders will have the freedom to share their personal data on the platform. Data shared is encrypted and thescientist'scommunity can use it for predictive modeling. Internet of medical things (IoMT), is another important aspect that can revolutionize healthcare by collecting patient data remotely share with stakeholders for continuous analyzing it and keep track of the patient's health. This includes the uploading of information on the platform, encryption, and used the integrated Blockchain to maintain the security and integrity, wipe out the information. Companies are also collaborating to research the application of Artificial Intelligence on the existence of allergic reactions. Seeing the assuring result of Blockchain in every field of pharmaceutical, around 70% of all life sciences executives expect to have a blockchain-backed platform in their companies.

Discussions

given the exhilarating results of some of the best blockchain-backed platforms developed by some companies and their analysis, which even interested the Centre for Disease Control (US federal government agency) the impact of Blockchain on the pharmaceutical sector. Now, there are some points to discuss the competitive landscape of blockchain technology in the healthcare sector. Company's competitive advantage can be defined using parameters like a company overview, company snapshot, product portfolio, key strategic moves and developments, market share, profile, production and share by player, mergers & acquisition, expansion, market vendor ranking analysis. The common characters of market segmentation like common interests, global market share, the supply of access control devices, and worldwide demand are being considered. Also, the production value and growth rate of blockchain technology can be compared in the healthcare market across different geographies. The application of Blockchain in health care supply chain management, interoperability, and exchange of clinical data records, billing, and claims management, other issues can be implemented globally. Healthcare payers, healthcare providers, other end users can be benefitted using blockchain technology.

Analysis of global blockchain technology application in the healthcare sector can be done region wise which includes the US, Canada and Mexico, Germany, France, UK, Russia and Italy, china,japan, India, and Southeast Asia and Saudi Arabia, Nigeria, Egypt and South Africa.

An exploration by specialists ascertains the significant aspects of the blockchain technology in the pharma sector. Its in-depth valuation for the coming time evolution can be derived using the past data and present situation of blockchain technology in the healthcare market situation.

Several studies on Blockchain were conducted to investigate ideas, market players, geographical locations, categories of products, and end customers in the market. Research study on global blockchain technology comprises primary and secondary data, which is exemplified in the form of research papers, products developed using Blockchain, pilot projects run, and reference diagrams. The study on blockchain technology has shown a structured style to involve basic dialect, blockchain technology in the healthcare sector, strength, limitations, and comprehension been discussed. The objectives covered in analyzing blockchain technology are in healthcare space, manufacturing, usefulness, utilization, position, and future pre-

diction. It also covers the healthcare market's potential advantages, opportunities, and challenges, restraints, and risks. It also focuses on healthcare producers, to capacity analysis, manufacturing, usefulness, number of customers, and forecast future planning. To analyze the opportunities in the blockchain technology in the healthcare sector for healthcare providers as well as patients, it needs to identify the rising segment. Studying competitive growth such as augmentation, consensus, floating new products, and purchases in the market. It has identified notable swing and components controlling the blockchain technology in healthcare market growth. It deliberately analyses every economic opportunity with respect to individual rising augmentation and their offering to blockchain technology in the healthcare market. Studies have also shown that blockchain technology development has been impacted by the COVID-19 in the pharma sector. Rising monetary stimulus and support of the government in the form of regulations across the globe has been mainly driving the utility-owned segment. It is being anticipated that the three largest economies of Asia will be impacted the most due to the covid-19 pandemic. Being the epicenter of this fatal disease, china is also the largest producer and supplier of drugs API to the rest of the world. Keeping accuracy in medical trials is a tough business. The cost of clinical trials/studies conducted over a longer period is a well-known challenge to pharmaceutical companies. Current, it is complicated to capture the holistic cost picture of the clinical trials since currents tools are not efficient enough.

Blockchain technology has shown promising results in bookkeeping clinical trials and financial assets efficiently. One of the major challenges that the pharma sector is facing today to choose the right person for the clinical trials. A large sum of money and a huge amount of time is spent to find qualified and onboarding candidates for clinical trials. Of all the drugs researched, only 10% of them make it to the market since it is proved very much difficult to identify the qualified candidate for the trials. While Blockchain might do not much fix this problem but its features of data integrity, security, privacy can be helpful to maintain interoperability for the pharma sector. The use of unique identification code backed by blockchain technology will make the matching of information related to patient clinical trials more efficient, faster, and cost-effective.

Solution to Management Consent Mess

To obtain permissions, options, and informed consent from patients upholds the concerns of data privacy and management in terms of transparency and data processing. Blockchain being the distributed ledger, has helped in assuring the candidates who selected for clinical trials by sharing the data in an immutable manner, keeping track of information processing. For the rapid processing of user data, a blockchain-backed platform that serves the stage for a rapid generation, sharing, and management of patient and healthcare data has been developed and tested. The insurance sector can be one of the major beneficiaries by developing smart contracts in B2B processes. To eliminate the counterfeit claims and make the claim system patient-friendly simultaneously, smart contracts can be developed to process, receive claims, and send payments. The claim and transaction cycle can be automated and help both the patients and the healthcare providers. It's not only the counterfeiting drugs but also the unlicensed physicians that have undermined the healthcare sector image. Bogus physicians can be eliminated from the healthcare system by building a credential verification system for physicians using a hashed code to prove they are indeed, licensed to operate. An information system can be developed to allow hospitals and healthcare institutions to exchange and access verified credential information which can also be used to develop a platform to share immutable information among all the healthcare providers. Another important aspect to be discussed with respect to is medication adherence. The medical adherence system needs to be developed to not only ensure the prevention of overdose and safety of patients but also enable industry to check the huge sum of money currently going wasted. It has been estimated that the system has the potential to save millions of dollars and euros around the world and the UK, respectively.

Conclusion and recommendations

Research study across various blockchain-based products, pilot projects, and the potential of Blockchain to overcome existing challenges seems to be pragmatic, which results nowadays in gaining notable recognition from individuals as well as organizations in the pharma sector dealing in different fields and dimensions.

It has the potential to transform the current industry with its features, which include anonymity, decen-

tralization, auditable, and persistence. It is expected that the current healthcare system will be reshaped by blockchain technology. The process will become more transparent, secured, and the resultant increase in the quality of healthcare at a lower cost. Till now, various Blockchain- backed products and pilot projects have been discussed in the healthcare industry and recognized the major research initiatives as well as future research opportunities. Precisely, tried to present research on health data management and how Blockchain will help to empower patients and streamline the health data sharing process. It is true that the view on an individual's privacy varies from country to country based on government regulations. Hence, it is urgent to research on standardization, regularization, and data retrieving data policies across borders along with retention and Strengthening transparency of clinical trial data and issues related to trust degradation can be addressed using blockchain technology. Findings of researches have proposed the use of Blockchain to improve the credibility of scientific findings from clinical trials and undermining problems of data missing and selective publications.

Issues of tracking drugs have been discussed; to deliver the timely, authenticated, and ensure the legitimate flow of drugs to the patients, pharmacists and healthcare providers can be assisted by blockchain technology as an indispensable tool. However, to implement robust tracking systems that can monitor the registration of the products, more research is required. Serialization is being used in current tracking systems which are not immune from tampering because codes embedded have fixed values that can easily be modified and tampered with by the counterfeiters in the current complex supply chain process. Billing and payment management are other such issues which are also included in the blockchain delivery system and must be secured. Issues related to claims and billing have seen continuous abuse by both patients and institutions in the healthcare, but Blockchain has the potential to resolve and diminish being a transparent system. So, the application of Blockchain in healthcare systems will be presented in the form of various devices connecting patients like wearable devices, remote healthcare services, etc., with their caregivers. Data is constantly generated in these systems and may be prone to hostile attacks while the communication network is processing it at various levels. There is a need to address this challenge and requires duo attention of researchers to how complex and diverse communication networks blockchain will be operated. Communication networks used by IoMT (Internet of Medical Things) delivery systems will be owned with different data access control policies by different service providers. It is needed to research and investigate blockchain mechanisms to promote one global access policy for the whole network to work in such an environment. More research is required on innovative solutions to allow intermediaries like devices, networks, etc. of the IoMT to promote Blockchain as a service and access basic coherent blockchain infrastructures.

Limitations

besides the good and positive results of many blockchain-based products developed to assess the technology, the study finds this technology is still on the verge of improvement rather than completed. Before adopting it to use in the pharmaceutical sector, many challenges must be addressed. The ***foremost*** challenge is to bring integrity and privacy. Since anyone can see anything on a blockchain network, it is believed that the storage of medical data itself is off-chain and blockchain stores only the hash code of the tag information. ***Secondly***, the challenge of bringing scalability and speed. In various studies conducted, it is shown that the speed of processing transactions is very low compared to that of the conventional way, let's say credit card. With time, the number of transaction volumes enormously, hence, it needs to be revolutionized. ***Thirdly***, chances of threat which risks attack to about more than fifty percent though it is theoretical but possesses plausible risk for which clear solution must be suggested. The availability of proof of work was limited, no real use cases were there to suggest the application of technology will revolutionize the healthcare. Only some prototype of products based on blockchain technology developed by some companies and pilot projects run has been used to assess the technology. In the case of data sharing, only EU data law, clearly provides the data sharing protocol in the legitimate manner which is written and can be studied. It is still rather a belief in the success of some products backed by Blockchain rather than any real case study. A blockchain-based product has been failed to provide energy efficiency and enough privacy for patient's identity. For electronic health records (EHR) of the patient's location, there is no study to suggest when to retrieve it. Breadcrumbs and high storage mechanisms look up a single record. There was no

consideration of access control and exhaustive authorization. The exact cost of blockchain-based products is not known. To improve the transparency of trials and maintenance of smart contracts and clinical records can be hindered because of significant scalability concerns. For transparency in the maintenance of records and creating surveillance nets, operation cost is not defined. Due to the absence of any rule to regulate blockchain use in the healthcare industry, there is uncertainty as to how a new policy framework will regulate privacy issues to use Blockchain in healthcare IleshDattani and Institution of Engineering and ***Fourth*** is the ownership of the data. Since Blockchain is decentralized, it is in some cases may be necessary to know who will regulate or grant the permission of data sharing. A huge amount of storage is required to store healthcare data like images, trial data, lab reports, and records of transactions in the blockchain network. As per the blockchain concept, every member of the chain will have complete access to the medical records of every individual on the chain, and these volumes have high storage capacity which exceeds current blockchain technology storage. The concept of Blockchain is not widely known yet, and it still depends on some successful stories carried in the form few products developed or pilot projects run. Currently developed and followed blockchain models are not successful, which can create an uncertain situation while implementing this technology and hence, become a major challenge. While Blockchain is a patient-driven network and patients will have full ownership of their data, but the reality is patient information will be validated by the companies supporting the patients. This results in hindering the progress due to confusion over the public use of Blockchain. Excessive use of energy while creating a new block is another hindrance. In the world, where current energy generation is the climate issue, the use of Blockchain won't make sense. Another issue with network security, in the case of bitcoin it was seen that miners who maintain the stability and security of network if they assemble coven, let's say >50%, then they can alter or rewrite the transaction, hence the security of transaction disappears. There is also concern that Blockchain is not indestructible, since in case of absence of any centralized authority or control point, in any uncertainty, no one is there who can go to close the Blockchain. Self-maintenance is required,and users must maintain their wallet else they may lose information. Blockchain is new to understand, not many are comfortable, that's why while tech teams are testing blockchain technology, but they seem hesitant when to move in full use. Still, the true nature of technology is not known, and this is the most challenging factor for the successful implantation of blockchain technology in the healthcare industry due to the absence of decent infrastructure,interconnectivity, and experts are needed. Interoperability, the computer systems able to make use of information is low in healthcare data which can cause damage to facilities given to patients.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Five decades of risk perception measurements of tobacco use: a review of literature

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Abstract

Perceptions of risk are beliefs about the likelihood of damage or loss. People make subjective judgments regarding the intensity and features of a danger. Smoking start and continuation are influenced by risk perception. Risk perception of tobacco use or smoking has always been controversial. Few studies found that risk perception is overestimated by smokers and tobacco users, while other studies found that smokers underestimate the risk of smoking. It has been observed that different authors have been using different approaches to measure the risk perception of tobacco use. The present literature review is an ontological exploration of the process of calculating this construct and determining which method gives more holistic and robust information. A literature survey was carried out to understand different ways in which risk perception can be measured. Fifty-seven studies were identified from 1970 to 2020 in which risk perception was calculated for any form of tobacco use. The literature review found that the researchers used two practical approaches to measure risk perception. In the first approach, the researchers tried to measure only the health risks of tobacco use, and in the second, multiple dimensions of tobacco use were measured. Most commonly perceived addiction and then the social risk of tobacco use was accessed. Though recent literature is dominated by an approach where a single dimension, i.e., perceived health risk of tobacco use, is most commonly access, it is inferring from the available literature that tools that access multiple sizes of the perceived risk of tobacco use give more comprehensive and robust information about that construct which can be used further to create tobacco use prevention intervention.

Keywords

Tobacco, Risk perception, Prevention, Experience, Addiction

Imprint

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Introduction

The theory of risk perception is valuable in helping us to understand the behavior of tobacco users. An awareness of the potential risks is an essential prerequisite to some health-related actions, and other activities experts suggest for handling or avoiding dangers. Beliefs regarding possible damage or the prospect of loss are known as risk perceptions. People's subjective assessment of the features and severity of danger is dependent on factors, including the context and how the problem was caused [1]. It is a personal evaluation of the likelihood of a certain kind of accident and how individuals are worried about the repercussions. [2] Many individuals have different definitions of danger, and how they see it depends on their surroundings and cultural values [3]. Scary experience is a common concept in everyday speech [4]. 'The likelihood of an unfavorable event occurring is part of what defines risk.' "a scenario or occurrence when anything of human worth is at stake and where the result is uncertain" [5]. The National Safety Council defines risk as "a measure of the likelihood and severity of the unfavorable effect." Health belief models such as both directly and indirectly [6]. Motivation theory for self-protection model of self-regulation Reason action theory proposed behavior theory cognitive social theory the theories of social control and social action Of these ideas, only the HBM, Protection Motivation Theory, and Self-Regulation Model utilize risk perception as a concept [7].

The perceived risk index is associated with smoking initiation among current nonsmokers. Perceiving smoking as a health risk reduces the chances of a young person initiating it [8]. Risk perception has repeatedly been identified [9]. Low perceived risk undermines the effects of health education and can influence treatment-seeking behavior [10]. It may even restrict an individual from opting for a cessation program. Further studies have suggested that behavioral intervention that enhances risk perception may benefit smokers and help them quit smoking.

Adults and adolescents perceive risk in different ways [11]. Adolescents minimize the risk associated with activities that can lead to harm, and thus this behavior leads to adolescents pursuing harmful activities like drug abuse, smoking, and binge drinking [12]. Another study conducted by Moffat and colleagues concluded that adolescents who engage in risky behavior do not fully realize the harm they expose themselves to [13]. Above mentioned findings demonstrate that adolescents perceive risk differently than adults as they underestimate the risks involved and lack awareness of the harm they expose themselves to by indulging in such behavior [14]. This further shows that adolescents are more vulnerable to get involved in risky behaviours like smoking tobacco compared to adults [15].

Risk perception of tobacco use or smoking has always been controversial. Few studies found that risk perception is overestimated by smokers and tobacco users, so there is no need to address it further during tobacco control efforts. While other studies found that smokers underestimate the risk of smoking which makes it vital to emphasize the risks during tobacco control efforts [16]. As mentioned by Weinstein, which reflects values, symbols, and ideology [17]. Weinstein demonstrates that the reason for these contradictory sets of results is due to how risk perception is measured. The present review is an ontological exploration of the measurement of the perceived risk of tobacco use [18]. Authors look at the five-decade journey of measurement of risk perception of tobacco use to understand which approach is useful to measure a more comprehensible and robust measurement of this construct which can be used further in the development of the intervention module [19].

Methodology

Databases for search

The following databases were used to choose peer-reviewed articles that were published -> The databases chose the published papers from among peer-reviewed publications. Research papers and treatments were located by using PubMed, Medline, Cochrane, Psych-info, JSTOR, EBSCO, and Google Scholar.

Studies utilising the following databases were done: risk perception, tobacco usage, perceived risk, perceived harm, risk estimate, and smoking. These phrases are used individually as well as together. All relevant research material was reviewed. Unnecessary and redundant information was removed from the research.

Literature review strategy

- Using the population of interest and exclusion criteria, exclude the research.
- Disqualify based on the Abstract.
- Based on the entire content and methods, exclude the research.
- Determined which method should be utilised in light of the literature review's goals.
- Compose the primary body of the literature review.
- Conclude a review by writing a conclusion on the literature that was utilised.

A literature survey was carried out to understand different ways in which risk perception can be measured [20]. Fifty-seven studies were identified from 1970 to 2020 in which risk perception was measured for any form of tobacco use. Figure 1 describes the number of studies measuring the risk perception of tobacco for over fifty years. In the present review Figure 2 explains the thematic arrangement of the review.

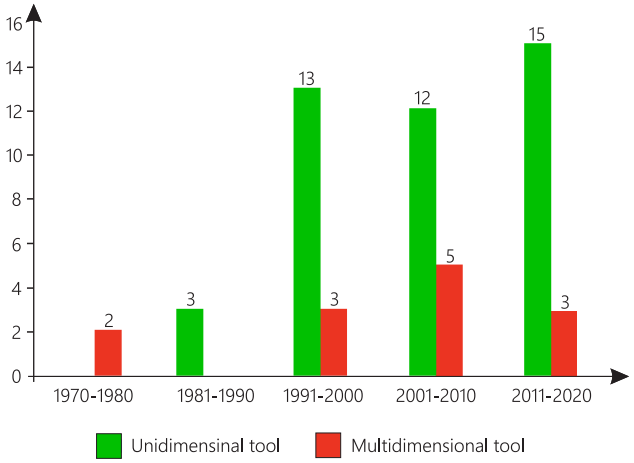

Figure 1. Risk perception measurement publications in the last five decades

Results

Framing the review under different themes

Various studies conducted in different populations assess diverse dimensions of risk perception. The present review tries to explore these studies and their approaches to measuring risk perception of tobacco use [21]. What different dimensions of risk perceptions of tobacco use were assessed? Tools and questionnaires used for different age groups, different types of tobacco use like smoking, smokeless tobacco, and waterpipe

smoking, and different health status of the population were included in the review [22].

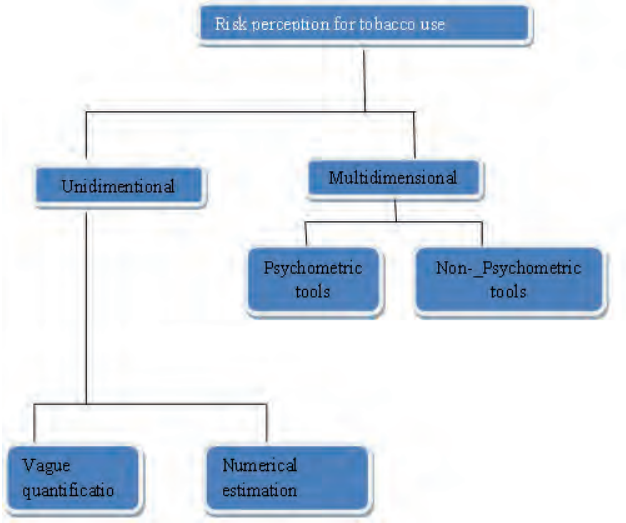

Figure 2. Arrangement of the review

Two major approaches were used by the researchers to measure the risk perception. In the first approach, the researchers tried to measure only the health risks of tobacco use, and in the second, multiple dimensions of tobacco use were measured [23]. As depicted in figure 2, health risk related to tobacco use was measured in two different ways, 'numerical or quantitative risk estimation' and 'vague quantification'. Studies using more than one dimension of risk perception were explored and divided based on their psychometric validation [24].

Assessment of the single dimension risk perception of tobacco use

Unidimensional studies, as the name suggests, are those that measure only a single dimension of risk perception of tobacco use [25]. Most of the studies only measure the health risk associated with tobacco use. Unidimensional studies were further divided based on the methodological to assess the risk perception of tobacco use, like vague quantification and numerical estimation [26]. had conducted a review of studies exploring the health risks of smoking cigarettes, in his book gives details regarding some studies with the same objectives. The current review does not contain any unpublished data or data from studies conducted by industries [27].

Numerical (quantitative) estimation of risk perception

Table no. 1 lists the studies on risk estimation of tobacco use, in which risk perception was measured

Table 1

Studies which assess the health risk of tobacco use (unidimensional assessment)

	Author and year	Numerical risk perception/ Vague quantification (or) Likert type/ Other	Sample size and/ or information of the population	Details about risk perception assessment
1.	Kristiansen, Harding& Eiser; 1983	Numerical estimate		0 to 100 scale; How likely to smoker/nonsmoker die of lung cancer : 0=not at all likey and 100= extremely likely)
		Numerical estimate		Person is dead how likely it is that he was a smoker
2.	Lee;1989	Numerical estimate	Seven smokers and 95 nonsmokers (age range, 15-65 years)	0 to 100 scale; 0= never to 100= certain: the related likelihood of heart diseases/ lung cancer/ bronchitis stroke.
3.	Viscusi;1990	Numerical estimate	3119	0 to 100 scale; how many smokers will get lung cancer out of 100?
4.	Viscusi;1991	Numerical estimate	a national survey of smoking behavior by a New York the research firm, Audits and Survey	0 to 100 scale; how many smokers will get lung cancer out of 100?
5.	Reppucci, 1991	Vague quantification	Two studies) 54 smokers and 304 nonsmokers b) 33 smokers and 299 nonsmokers	7-Point likertscale:-Comparing their risk of developing lung cancer to that of other students at their school
6.	Greening;1991	Vague quantification (Logarithmic rating	408	Subjective probability of fatality was assessed using a logarithmic type rating scale ranging from

	Author and year	Numerical risk perception/ Vague quantification (or) Likert type/ Other	Sample size and/ or information of the population	Details about risk perception assessment
		scale)		0 to 6. Subjects were asked to evaluate the chance that "someone like you" would die from the 24 reasons mentioned in the survey.
7.	McKenna 1993	Numerical estimate		0 to 100 scale
8.	Chapman;1993	Vague quantification	745	consequences of smoking
9.	Strecher;1995	Vague quantification	2785	7-Point Likert scale:- compare to others rate the risk of heart attack stroke or cancer
10.	Schoenbrun;1997	Numerical estimate	9825	chance of living 75 years and more 0= no chance at all and 10= absolutely certain
11.	Borland; 1997	Numerical estimate	Four annual surveys of smoking behavior of age 16 years and over 1st; 654: 2nd; 635: 3rd; 623: 4th; 596	What percentage of smokers die from reasons directly linked to their smoking?
		Numerical estimate		11- On a scale of one to one hundred percent probability, how likely is it that smoking will cause you to die?
12.	Sutton ;1998	Numerical estimate	1625	0 to 1000 scale; smokers killed before age 70; cut off was 250
13.	Hahn;1998	Vague quantification	154	7-Point Likert scale:- Chances of developing lung cancer compare to other people
14.	Resnicow et al. 1999	Vague quantification	2,600 respondent	4-point scale from no risk to great risk
15.	Slovic P;2000	Vague quantification	321	4-point scale from strongly agree to disagree strongly
16.	Antonanzas et al.2000	Numerical estimates	2571	Utmost 100 cigarette smokers
17.	Krosnick 2001	Numerical estimate	4473	How many of 1000 randomly selected American individuals who smoked one packet of cigarettes every day for 20 years when they were 20 years old will get lung cancer at some point throughout their lives?
18.	Romer and Jamieson;2001	Numerical estimate	300 smokers and 300 nonsmokers	How many of every 100 cigarette smokers do you estimate will: (a) get lung cancer as a result of their smoking? (b) Have cardiac issues, such as a heart attack, as a result of their smoking? (c) Pass away as a result of a smoking-related illness?"
19.	Power, Neilson, Perry;2004	Numerical estimate	1247 adults and 171 General Practitioner	How many do you estimate will be killed on average out of 1,000 20-year-olds in Ireland who smoke frequently and continue to smoke?
20.	Rebecca Murphy-Hoefer, Stephen Alder, Cheryl Higbee;2004	Vague quantification	1020	4- point likertscale:-Students were asked to respond with a definite yes, a likely yes, a likely no, or a definite no.
21.	Weinstein, Marcus, Moser 2005	Vague quantification	6369 Participants; 1245 current smokers	5- point Likert scale :- 'How likely do you believe the typical (male/female) cigarette smoker will get lung cancer in the future?" "Very low" was one of the answer choices, and the numerical code given to it was "very low." 1, "a little low" 2, moderate" 3, "fairly high" 4 or "extremely high" 5.
22.	Peretti-Watel, Constance, Guilbert, Gauti er, Beck, Moatti;2007	Numerical estimate	3820; 979 current smokers	'According to you, a smoker who smokes how many cigarettes per day is a danger of developing cancer as a result of smoking?' ''And according to you, after how many years is someone who smokes N cigarettes per day at high risk of cancer?" they were asked for a specific answer N.

	Author and year	Numerical risk perception/ Vague quantification (or) Likert type/ Other	Sample size and/ or information of the population	Details about risk perception assessment
23.	Lundborg;2008	Numerical estimate	8592 Swedish adolescents aged 15–18	0 to 100 scale; How many smokers do you estimate will die from illnesses related to their smoking in a group of 100?
24.	Viscusi and Hakes;2008	Numerical estimate	1013;1997 national survey USA	1) 0 to 100 scale;How many of a hundred cigarette smokers do you estimate will die from lung cancer, heart disease, throat cancer, or any other ailment as a result of smoking?
		Numerical estimate	1002; 1998 Massachusetts survey	2) How many smokers do you believe will get lung cancer as a result of their habit?
25.	Song et al 2009	Numerical estimation	395	Every day, you smoke approximately 2 or 3 cigarettes. You smoke alone at times and with others at other times." Participants assessed the likelihood (from 0% to 100%, as indicated by the participant) that they would personally experience each of the following smoking-related negative effects in the provided hypothetical situations.
26.	Brown ak;2009	Vague quantification	804	A single item reflecting attitudes about the harms produced by smoking, assessed on a 5-point scale, was used to assess perceived risk from smoking. A score of 1 meant that people's health was harmed as soon as they started smoking, while a score of 5 meant that individuals had to smoke for years before their health was harmed.
27.	Ferrante et al., 2010	Numerical estimation	1700	How many cigarettes/day are acceptable from a health hazard point of view?"
28.	Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2010).	Vague quantification		3-point Likert scale:-"How much of a physical or other danger does occasional smoking pose?" and "how much of a physical or other risk does smoking 1–2 packs per day pose?" were the two queries. Both questions were evaluated on a scale of 0 to 3 (no risk) and added together to produce a single perceived risk of smoking score (range 0–6).
29.	Doran N:2011	Vague quantification	1688	3-point Likert scale:-"How much of a physical or other danger does occasional smoking pose?" and "how much of a physical or other risk does smoking 1–2 packs per day pose?" were the two queries. Both questions were evaluated on a scale of 0 to 3 (no risk) and added together to produce a single perceived risk of smoking score (range 0–6).
30.	Gerkin;2012	Numerical estimate	14 to 22 years	How many people will die from lung cancer out of every 100 cigarette smokers that smoke throughout their adult lives? 2) How many nonsmokers will die of lung cancer if they never smoke and do not live with a smoker? 3) Is it harmful to your health to smoke every day? a four-point scale
31.	Harris JK;2012	Vague quantification	Smokers current, on current and nonsmokers Bosnian people in the US;499	5-point Likert scale
32.	White LJ;2012	Vague quantification	Smokers and nonsmokers;507	28-item questionnaire
33.	Daniels and Roman;2013*	Vague quantification	health-risk of smoking the waterpipe_389	5-point Likert:- (Missouri College Health Behavior Survey (MCHBS, 2010-2011)) compare relative risk of waterpipe smoking with smoking
34.	Heinz Aj;2013*	Vague quantification	143 ethnically diverse undergraduate students	3-point Likert scale:- compare relative risk of waterpipe smoking with smoking

	Author and year	Numerical risk perception/ Vague quantification (or) Likert type/ Other	Sample size and/ or information of the population	Details about risk perception assessment
35.	Strong DR;2019	Vague quantification	13651, 12-17 yrs	4 point scale collapse in 3 point
36.	McKelvey K;2018	Numerical estimation	445, 19.3(1.7) Mean age (SD)	Perceived likelihood (from 0% to 100%) of encountering certain health and social hazards
37.	Wiener RC;2020	Vague quantification	4,308,12 yrs to 18 yrs	
38.	Pericot-Valverde I;2017	Vague quantification	3738, age <or =49	"How dangerous do you believe e-cigarettes are to one's health?" "Not at all," "moderately harmful," and "extremely harmful," respectively.
39.	Leavens ELS;2019	Vague quantification	792,Age 19.64 (SD = 2.84)	"How many do you estimate will develop cardiac issues out of every 100 cigarette smokers/ nonsmokers?"
40	Popova L ;2018	Vague quantification	5398, Age 18 years and above	A seven-point Likert scale is used to assess risk perceptions of various health risks, with 0 indicating no possibility and 6 indicating a very high probability, as well as a distinct category of 'I don't Know'.
41	Parker, MA;2018	Vague quantification	10081 Age Below 18 years	To determine the absolute damage of various cigarette products, three categories were used: "no or little harm," "some harm," and "a lot of harm."
42	Pacek LR; 2018	Vague quantification	2006–2015 National Survey on Drug Use and Health (NSDUH)559,613	From "no danger" to "high risk" on a four-point Likert scale
43	Rayens MK; 2017	Vague quantification	667 University student	A three-point Likert scale was used. 'A serious health danger,' says the report. 'Moderate health risk,' 'Minor health risk,' or 'No health risk as all.'

using subjective probability and estimated using numeric scales [28]. For example, a study assessed risk perception of tobacco use by asking the participants the number of smokers suffering from lung cancer among 100 smokers [29]. Kristiansen and his colleagues published a study that used a numerical risk estimation of tobacco use. This method of estimation was similar to that used [30], and in several of his studies after that. For smoking, the risk was calculated using a 0 to 100 scale, with 0 indicating that lung cancer is very unlikely to occur and 100 indicating that it is quite probable [31]. Few studies deviated from the abovementioned scale values and used values ranging from 0 to 1000 or 0 to 10 to estimate the probability.

All studies assessed the health risk of tobacco use either by calculating the probability estimates of people suffering from or dying due to lung cancer [32]. Most of the studies were based on lung cancer, but few included more than one illness like heart disease and throat cancer. Some authors added another dimension such as age and calculated the probability of the occurrence of a health hazard or death mostly after the age of 70 years [33]. Recently studies have shown to use a different technique in which they measure the number of cigarettes required to cause cancer instead of the probability of cancer or death. These kinds of studies are few but show a recent change in the approach taken to assess the risk perception of tobacco use [34]. Song and colleagues used a very unique approach to assess the risk perception of tobacco use. They asked the consumption of a particular number of cigarettes for a particular number of years. the average subjective risk estimation of the occurrence of lung cancer among smokers in which risk was estimated using numerical estimation [35]. His analysis demonstrated that there was an overestimation of risk perception in all the studies where data was collected by telephonic interviews [36]. Studies in which the data was collected by face-to-face interviews reflected a lower average value of risk perception. Thus, according to him, the cognitive effort required in giving answers to different data collection techniques may be the factor behind the overestimation of risk perception by numerical estimation [37]. Weinstein mentioned another reason accountable for the variations in risk perception estimation. He stated that differences in estimation oc-

curred when participants and risk of others in general [38]. Optimistic bias leads to lower risk estimation for self, compared to others' risk estimation. Most of the studies in Table 1 assess the risk perception of smokers in general. Only a few studies asked its participants to assume that they were smokers and to self-estimate their risk perception [39]. This explains the underestimation of the risk perception reported in this study [40]. Most of these studies involving the numerical estimation of risk perception of tobacco use focused on smoking of tobacco, more particularly cigarette smoking [41]. None of these studies investigated or compared the risks associated with smokeless tobacco products. However, upon examination of the geographic distribution of these studies, it became apparent that the majority were conducted in industrialised western nations where cigarette smoking is the most prevalent type of tobacco use.

Estimation of risk perception of tobacco use by vague quantification

Vague quantification studies are listed in appendix 1. Most of these studies used Likert type items to assess the perceived risk of tobacco use, even though they lacked uniformity in the forms of Likert type items used in the studies. A thorough review of these studies revealed that 3 to 7 point Likert type items were used. A maximum number of studies used the 7 point Likert type items. Vague quantification studies assess only a single dimension, i.e., health risk related to the use of tobacco. The most commonly used fatal illness to assess health risk perception related to tobacco use was lung cancer, but heart diseases and stroke were also used in addition to lung cancer by many researchers. The majority of research contrasted smokers' and nonsmokers' risk perceptions. Several studies also compared smokers' self-perceptions of risk to those of nonsmokers. Few research have examined whether smokers and nonsmokers accurately evaluate the danger associated with tobacco use. Among the research that examined smokers' and nonsmokers' risk perceptions about tobacco use most of them revealed that a smoker underestimates the risk of lung cancer compared to a nonsmoker. This misunderstanding further study conducted showed that a heavy smoker rates his risk lower than that of an occasional smoker. Only two studies from Strecher and colleagues and White and colleagues demonstrated that smokers perceived higher risk of fatal illness due to smoking than nonsmokers. Risk perception of death did not differ between smokers and nonsmokers. Studies that compared the smokers' risk perception with other smokers showed mixed results. Bosnian refugees showed that the smokers' perception of their own risk of developing a fatal illness was less than other smokers' or average smokers' perception. These results about the underestimation of risk may be due to an optimistic bias and feeling of invulnerability among the users.

Assessment of multiple dimensions of risk perception of tobacco use

Risk perception is a quantifiable, predictable, and multidimensional phenomenon. The psychometric approach has been widely used to create scales for the measurement of risk perception for various activities. concluded from their studies that perceived risk can be predicted from five components like financial, physical I and physical II, psychological, and social risk. In Mettler tried to assess the smoking attitude and behavior using the five-point Likert scale. The research examined the health effects of smoking and the connection between smoking and one's social life. Table 2 summarises research that examines several aspects of risk perception and provides data on the various characteristics they examine. The majority of research examined risk perception in addition to many other psychological variables associated with smoking. Several studies have also attempted to investigate distinct aspects of risk perception, such as addiction risk, financial risk, and social risk, either alone or in combination. Branden and Becker developed the Smoking Consequences Questionnaire (SCQ) in 1991, using a psychometric method to evaluate smokers' multidimensional perceptions of smoking. Harmful effects, social encouragement, differential punishment, and fat burning were identified as the main variables preserved in their study. The research classified smoking-related effects into sixteen groups, including health risk, persistent addiction, and social impact. The SCQ was modified and validated for the adult population by Copeland and colleagues. As a consequence, the number of variables in the original SCQ was increased from four to eleven in the SCQ for adults. Rindfleisch and Crockett created a questionnaire in 1999 to assess five distinct kinds of risk perceptions associated with cigarette smoking among adolescents, including addiction, financial, health, time, and social risk. Budd and Preston created an assessment

Table 2

Multi dimentionalassesment of the risk perception of tobacco use

Sr. No.	Author and year	Sample size and/ or information of population	Psycho-metric validation (Yes/No)	Dimensions of risk perception	Name of scale
1	Jacob Jacoby and Leon B. Kaplan;1972	148/ upper-class enrolled in Consumer Psychology	No	perceived risk emerged.	NA
2	Curt mettlin ;1973	156/college undergraduates and their significant others	No	(1) the inconvenient nature of cigarette smoking; (2) the pleasure received from smoking; (3) the health risks associated with smoking; and (4) the link between smoking and one's social life.	NA
3	Brandon and Becker ;1991	1502/ students	Yes	There were four variables that were kept. 1) Harmful Consequences 2) Consistent positive reinforcement 3) Reinforcement of negative behaviour 4) Controlling appetite and weight	The smoking consequences questionnaire
4	Amy L. Copeland, Thomas H. Brandon, and Edward P. Quinn;1995		Yes	1) Reduction of Negative Affect 2) Stimulation/State Boosting 3) Risk to one's health 4) Sensorimotor Manipulation/Taste Manipulation 5) Sensorimotor Manipulation/Taste Manipulation 6) Facilitation of social interactions 7) Weight Management 8) Craving/Addiction 9) Physical Negative Feelings 10)Decreased Boredom Negative Social Impression (No. 11)	The Smoking Consequences Questionnaire-Adult
5	Rindfleisch and Crocke;1999	292/college students, 18 to 25 years of age	Yes	1) Addiction 2) Financial 3) Health 4) Social, and 5) Time	NA
6	E.U. Weber, Ann-Rene, E BLAIS and N E. Betz;2002	211 women and 146 men	Yes	The six-factor solution could be interpreted as an 1) Investment, 2) gambling,3) health/safety, 4) recreational, ethics and 5) social risk factor	A Domain-specific Risk-attitude Scale: Measuring Risk Perceptions and Risk Behaviors
7	GM Budd, DB Preston;2001	172	Yes	1) Emotional Benefits 2)Health Hazards 3)Self-Confidence 4)Body Image	Perceived Consequences of Smoking scale
8	Johanna M. Lewis-Esquerre, James R. Rodrigue, Christopher W. Kahler;2005	437	Yes	1) Reduction of Negative Affect 3)Social facilitation 4)Weight regulation 2) Taste/sensorimotor manipulation 3)Social facilitation 5)Positive physical sensations 6)Decreased boredom 7) An unfavourable social impression	Adolescent Smoking Consequences Questionnaire
9	Sherry A. McKee, Stephanie S. O'Malley , Peter Salovey , SuchitraKrishnan-Sarin , Carolyn M. Mazure/2005	573	Yes	1) Risk perception: - a) Weight gain b) Negative emotions c) Attendance/ concentration d)Social exclusion e)Loss of pleasure f)Craving 2) Perceived advantage	Perceived Risks and Benefits Questionnaire (PRBQ) Associated with quitting smoking
10	Melinda F. Davis, N. Campbell, Dan Shapiro and Lee B. Sechrest;2006	215	No	chance of developing or have 12 different condition -3 much below average to 3 much above average	The Smoking Hazards Scale

Sr. No.	Author and year	Sample size and/ or information of population	Psycho-metric validation (Yes/No)	Dimensions of risk perception	Name of scale
11	Anjum;2008*	646	No	1) addiction 2)social and 3)health risk perception	NA
12	Lipkus IM;2011*	Study 1 (N = 91) Study 2 (N = 112)	No	1)Perceived harm 2) Perceived risk of addiction	NA
13	Aryal;2013	352	No	1) Physical danger I (lung cancer, heart disease, wrinkles, bad colds) 2) physical risk II (wrong toxicity, foul breath, respiratory problems); 3) social risk (stressing, stinking like an ashtray) and4) social benefit (looking cool, feeling relaxed, becoming popular, and feeling grown-up).	NA
14	P. Salameh, , J. Salamé, M. Waked, B. Barbour, N. Zeidan, and I. Baldi ;2014	3384	Yes	1) carelessness (doing something without thinking about the repercussions and being irresponsible); 2) novelty and sensation seeking 3)hedonistic motivations 4)social desirability 5)achievement of future objectives and success 6)Seeking popularity.	Risk perception evaluation, risk participation, and risk perception scale

to help young people in determining their perceived effects of cigarette smoking. They based their findings on the SCQ on several aspects, including health risks, emotional benefits, self-confidence, and body image. created the Perceived Risks and Advantages Questionnaire (PRBQ) to assess risk perception and perceived benefits of smoking cessation. The PRBQ examined two key areas, namely risk perception and perceived benefits of smoking cessation. Further exploration of risk perception included questions regarding weight increase, adverse consequences, attention/concentration, social rejection, loss of pleasure, and desire.

Salameh and colleagues recently conducted a risk perception evaluation and created a risk participation and perception scale with Lebanese students. As the name implies, the scale assessed both risk participation and risk perception. This measure revealed six domains of risk perception: irresponsibility (without contemplating the repercussions and recklessness), novelty and experience seeking, hedonistic motivations, social desirability, future goal accomplishment, success, and popularity seeking. This is one of the few risk perception assessment instruments developed outside of Europe and America. Another significant feature of this scale is that it includes risk perception associated with waterpipe smoking, in contrast to previous measures established in the United States and Europe that concentrate only on cigarette smoking. investigated and quantified risk perceptions associated with cigarette smoking in Nepal by establishing four aspects of risk perception.

Risk perception of other forms of tobacco use

The most commonly used tobacco products for risk perception assessment were cigarettes, but few studies assessed the risk perception of waterpipe smoking as well. Results from both types of studies show that waterpipe smokertobacco. Most of these studies were published after the year 2000, suggested a shift in assessing risk for non-smoking tobacco products. A systematic review was conducted by Akl and colleagues, which explored the perception of waterpipe smoking along with motives and beliefs Anjum and colleagues conducted a study in which they explored addiction as well as social and health risk perception about waterpipe smoking. explored the addiction to water pipe smoking, but the study lacked any psychometric validation. Risk perception of tobacco differs significantly based on the type of tobacco products in question. There is not a single standardized scale available to access multiple dimensions for smokeless tobacco users or those with a habit of both smoking and using smokeless tobacco products. Since most of the tools were developed to use in the western world, there might be a serious limitation in using the same scale in Southeast Asian countries

based on their social contexts. The recent trend of multidimensional exploration of risk perception of tobacco use showed an increasing number of studies being conducted outside the USA and Europe compared to previous decades. Previously, most of the studies were focused on the risk perception assessment of cigarette use, but recently other tobacco products like e-cigarettes, water pipe (hookah) are being included. There is a need to develop a single scale that can assess the risk perception associated with different tobacco products and not only smoking.

Discussion

Multidimensional assessment of risk perception has been in use for quite a long time in risk perception research. Few scales have been developed and psychometrically validated to assess the risk perception of tobacco use. All these scales have limited applications in cases where risk perception has to be measured in different cultural contexts and different types of tobacco products. Most of these studies either focus on smokers' risk perception or compare the smokers' risk perception with other smokers' or nonsmokers'. There are very few studies that pay attention to the initiation and risk perception of smoking. Slovick concluded that risk perception plays a very limited role when it comes to initiation of smoking. Slovick rationalized that the health risk of smoking is perceived as a long term risk, i.e., whatever the consequences, they will occur years after the initiation of smoking. That is why risk perception plays a very limited role when it comes to the prevention of smoking initiation. Slovick's conclusion is based on unidirectional assessment (Health risk) of risk perception of tobacco use. As shown in Table no.1, these studies are mostly focused on collective risk, i.e., lung cancer or death. People initiating tobacco use will be less concerned with this risk as it takes many years for lung cancer to develop in smokers. Slovick stated misperception of this long term risk and unawareness about addiction risk are the major reasons behind smoking initiation. When it comes to the preparation of a comprehensive tobacco use intervention module, information is gathered using questions that assess the unidimensional risk perception of tobacco use, due to which it will have very limited use. It will not provide any information regarding the participant's perception of the addictive capacity of tobacco use.

A literature survey showed that there were two major approaches used by researchers to validate the scale used to measure the risk perception of tobacco use. In the first one, the researchers tried to measure the health risk of tobacco use, while in the second approach, multiple dimensions of tobacco use were measured. Further, the literature review has revealed that assessing holistic picture compared to the other studies which access a single dimension. It has also demonstrated that there are various psychometrically validated tools available to measure the risk perception of smoking. But as mentioned by Weinstein, risk perception, which reflects values. Helpern-Felcher also mentioned in her review that cultural. It is very important to reflect these factors in the tool. Thus tools should be culturally valid and socially acceptable. Second All tools are specifically designed to measure the risk perception of smoking tobacco. There is not a single tool available to measure risk perception for the use of smokeless or mixed tobacco products. A significant proportion of poly tobacco users who either uses smokeless tobacco products or both types of products.

Conclusion

When it comes to the preparation of a comprehensive tobacco use intervention module, information is gathered using questions that assess the unidimensional risk perception of tobacco use, due to which it will have very limited use. It will not provide any information regarding the participant's perception of the addictive capacity of tobacco use. Social risk and addiction risk can be important for tobacco intervention, but social risk perception can be sensitive to the cultural context of every society. As far as the measurement of the risk perception of tobacco use among adolescents from the different cultural setup is concerned.

1. The literature review provides the following suggestions
2. Multidimensional assessment of risk perception is necessary if the objective of the exercise is to utilize risk perception for tobacco intervention strategy
3. The psychometrically valid tool is necessary to increase external validity and reliability to the results
4. This tool should be able to measure social risk and addiction risk of tobacco use by understanding the social and cultural context of a particular society and mixed tobacco use (smoking and smokeless) practice among adolescents in those countries.

The current literature review has shown that at present, there is no such tool available in the published literature that can fulfil the above mention criteria.

It is necessary to develop and validate indigenous tools from scratch, which can correctly measure the multiple dimension of risk perception of tobacco use among adolescents. Measurement obtains from such a tool can be used to design a more appropriate and context-specific tobacco intervention module for adolescents from different cultural setup.

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REPORT

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Design of decision support system incorporating data mining algorithms for strengthening maternal and child health systems: Inclusion of systems-thinking approach

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Abstract

Reduction of maternal and infant mortality rates has been recognised as one of the important goals of this century. Both coverage improvement and inequity reduction have been set up as millennium targets. Despite the availability of effective interventions, maternal and child healthcare conditions are not improving in developing countries because of inefficiently functioning health systems. Knowledge generation about behaviors of health system building blocks on the implementation of several healthcare interventions will help policymakers to design situation-specific and strategic interventions. A decision support system has been devised incorporating data mining algorithms which would help to understand the condition of maternal and child healthcare indicators; educational, socio, and economic situations; healthcare status; and healthcare service blocks and their relationships with each other. In this paper, the design of the DSS has been discussed elaborately. To enhance a system-wide understanding of the healthcare system, all healthcare-related factors have been incorporated into this system. Three knowledge generation modules have been prepared by utilizing different visualization and data mining algorithms.

Keywords

Data mining, Health system, Decision support system, Maternal and child health care, Systems-thinking approach

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1. Introduction

Reduction of maternal and infant mortality rates and increase of availability of healthcare services both were declared as the targets in Millennium Development Goals (MDGs) (United Nations, 2013) and then in Sustainable Development Goals (SDGs) too (Chaudhuri, 2015). MCH indicators have improved worldwide in due course of time but did not achieve expectations. Moreover, countries with poor health conditions have witnessed very fewer improvements.

The primary reason for the slow progress of healthcare conditions in low and middle-income countries (LMICs) is the weak and fragmented health system which restricted the scaling up of healthcare interventions as per the desired volume. The coverages of interventions are still very poor in LMICs due to many reasons like lack of health workforce, healthcare infrastructure, finance, leadership, etc. Along with low coverage, inequity in healthcare services among the different socio-economic groups of people is also a major hurdle noticed in most of the developing countries.

With the help of advanced information technology and analytical techniques, issues regarding the MCH system can be resolved. A Decision Support System (DSS) has been devised to help healthcare managers for designing situation-specific strategic interventions by analysing different healthcare-related data. For generating the overall view of the system, all MCH related factors have been included in this platform. Three broad modules have been prepared in this system. The first module calculates descriptive statistics of each factor, measures correlations among factors, and develops figures through which the effect of healthcare interventions on different healthcare indicators throughout different socio-economic strata can be visualized. The second module identifies the high impact MCH interventions which had significant influences on MCH indicators and in the third module, internal associations among different health system factors get discovered. Different statistical and machine learning techniques have been utilized for developing these modules. In this paper, the design of the DSS has been described elaborately. By using the proposed DSS, healthcare managers will be able to make strategic interventions.

2. Background

2.1. Maternal and Child Health Indicators

Healthcare indicators have been devised to measure the healthcare condition of any region. In maternal and child healthcare, renowned indicators are Infant Mortality Ratio (IMR), Under-five Mortality Ratio (U5MR), and Maternal Mortality Ratio (MMR),. These are the major indicators gauged globally to understand maternal and child healthcare conditions. The fourth and fifth targets among eight MDGs were the reduction of child mortality and improvement of maternal health respectively (United Nations, 2013). MCH indicators have improved worldwide between 1990 and 2015 but did not achieve targets prepared at the Millennium summit. The UN General Assembly again prepared seventeen numbers of new targets named as Sustainable Development Goals (SDGs) (Chaudhuri, 2015) for achieving the unfinished agenda after 2015. The third target among the seventeen targets is specified for the healthy life of the population.

2.2. Maternal and Child Healthcare Interventions

The usage of effective interventions helps in reducing MCH indicators. Designing suitable interventions for both mothers and children is an important domain of research in healthcare. Previously treatments were concentrated on curing illnesses only but the importance of life course health development approach has got realized in around 1980s. Dr. Kerber and colleagues first developed a framework for integrating all MCH interventions throughout the continuum of care (Kerber et al., 2007). Two important dimensions have been incorporated in that framework. Those were the dimension of time and the dimension of place. Time dimension represented interventions applied at different stages of life either for mothers or children. Life stages dimensions have been classified *under adolescence and before pregnancy*, *pregnancy*, *birth*, *both postnatal for mother and child*, *infancy*, and *childhood* categories sequentially. The dimensions of place of the continuum have included all the places wherever healthcare should be provided. Those have been categorized under three broad segments – *clinical care*, *outreach and outpatient services*, and *family and community care*. Researchers have developed eight broad packages of interventions based on the life-stage and location where the services are provided. Under those packages, more than 190 separate interventions can be included.

Among eight packages, three packages are delivered at the clinical level, four packages are through outpatient and outreach services, and one package is for home and community care. Clinical care packages are for reproductive healthcare, childbirth care, and new-born baby and child clinical-care. Major clinical healthcare services for reproductive age group females are the treatment of sexually transmitted infections or HIV, safe-abortion, post-abortion care, gynecological emergencies, etc. Skilled attendant care for normal birth and obstetric care have been selected as priority interventions under the childbirth clinical-care package. In developing countries, the availability of skilled birth attendants was approximately 50% in 2006 (UNICEF, 2006). Now the rate has slightly improved but still very less with respect to standard requirements. New-born baby and child clinical-care package includes primary level clinical care for new-borns along with emergency services. Outreach and outpatient services have been classified into four packages namely reproductive health package, antenatal care package, postnatal care package, and child health package. In reproductive outreach and outpatient health package, educating adolescent girls and reproductive women regarding contraception, family planning methods, sexually transmitted diseases, HIV, etc. is the most important intervention. Interventions at this stage help to enhance knowledge on safety and healthy reproductive methods among adolescents and reproductive women. Antenatal package cares for women throughout her pregnancy. Women need at least four antenatal visits for safe and healthy infant birth. Screening and treatment of disorders (like anemia, hypertension, diabetes, malaria, etc.), provision of preventive interventions (tetanus immunization and insecticide-treated bednets), and imparting knowledge about emergency preparedness, HIV, birth, diet, hygiene are paramount interventions at this stage. The postnatal care package primarily includes healthcare services that start immediately after childbirth. First few hours after delivery are very crucial and maximum deaths happen within that period due to lack of healthcare support. Still in developing countries, the ratio of postnatal services is very alarming. Improvement of immunization and nutrition rates among new-borns is the major aim of the

interventions delivered through child health package at outreach and outpatient services. Lack of nutrition is one of the major reasons for child mortality rate. Improvement of early breastfeeding rates has also been included under that package. There is one package for family and community care. The main mission of this package is to improve the family behavioral aspect of child delivery. Major interventions under this package are knowledge generation about hygiene; immediate breastfeeding; knowledge about antenatal and postnatal services and the same for safe delivery; knowledge about emergency illnesses etc.

Maximum countries are now following this continuum of care packages for creating MCH infrastructure. Healthcare governing authority of India i.e. Ministry of Health and Family Welfare has also set up MCH interventions upon the continuum of care framework (Ministry of Health and Family Welfare. Government of India, 2013). Each of the above interventions has been incorporated in the proposed DSS under the MCH interventions category.

2.3. Health System

According to WHO, all organizations, people, and actions whose primary intent is to promote, restore, and maintain health altogether are called health system building blocks (WHO, 2007). The major goal of a health system is improving the health of a region by enhancing both coverage and equity and this can be possible by spreading healthcare interventions' reach to the needy people. It has been comprehended from the previous section that efficient interventions are available for the reduction of maternal and child deaths. Still, in majority LMICs, high mortality rates exist due to the inefficient functioning of the health system. Right now health system strengthening is one of the major issues globally and it will only be possible after creating a clear understanding of the health system.

The health systems, like other systems, are also the integration of different factors or blocks. There are many health system frameworks proposed by different researchers at different points of time. Andrew Cassels (Cassels, 1995) described the health system as a result of demand and supply which intermediary agencies influence. Julio Frenk (Frenk, 1994) classified the health system into five actors. Those were health care providers, people, the State, organizations generating and managing resources, and other healthcare-associated service sectors.

In WHO's 2007 report(WHO, 2007), the health system has been represented as the integration of six kinds of building blocks. Healthcare goals can be achieved by monitoring and designing sustainable strategies for all health system building blocks. Service delivery block represents safe, good quality services to everyone, especially the most needed, with optimum utilization of resources. Good service delivery in primary healthcare can be assured by maintaining demand for services, delivering packages of integrated services, developing proper infrastructure and logistics systems, and through good management with maximum reach to the last miles. The health workforce is another important pillar of the primary health system. Community-based services have been regarded as the most influential intervention for improvement of healthcare indicators which cannot be imagined without an efficient and skilled health workforce. Fair distribution of responsive and productive workforce throughout locations is always a great challenge for any health system provider. A well-performing health information system helps to assimilate data on health-related factors, analyze, and produce actionable insights on the performance of the health system. Medical technologies, products, and vaccines have also been regarded as one of the blocks of the health system. Ensuring equitable accessibility of medical products and vaccines should be taken care of by an efficient health system. Protecting financial risk is also a major task of a health system and finally, proper leadership or governance is required for the efficient unbiased working health system.

2.4. Obstacles in MCH services

Coverage and inequity are the most prominent obstacles that hinder the betterment of MCH, especially in LMICs. Victora and team observed that countries with higher socioeconomic inequalities have accounted for the lower improvement in healthcare services coverage by analyzing data from 75 countries with high mortality rates (Victora, Barros, et al., 2012). Many researchers worked to find out the determinants for inequity in the utilization of maternal and child healthcare services. Determinants like economic status, religious pressure, maternal education found out very significant factors, conducting a cross-sectional study in urban regions as well as in poor regions of Karnataka in India in 1993 (Bhatia & Cleland, 1995). Another study also observed the impact of mother's

education on the utilization of healthcare services in Thailand (Raghupathy, 1996). Studies have also detected the socio-economic disparity as one of the major determinants (Joe et al., 2010; A. Singh et al., 2012). Recently few studies have explained the significance of health system factors on the utilization of MCH interventions. A study conducted by P. K. Singh and the team revealed that the number of Primary Health Centers (PHC), availability of labour room, and registration of pregnancies under each district have relationships with the utilization of MCH services (P. K. Singh et al., 2014).

Anderson and Newman (Andersen & Newman, 1973) categorized all the determinants of inequity under three factors. Those were social factors, system factors, and individual factors. Social determinants include knowledge about health and illness as well as people's belief towards recovery services. Health service organizations were included under system factors and factors like family, community, society, demography, etc. have been considered under individual determinant.

In 2007, the WHO proposed a new framework for Social Determinants of Health (SDH) named as Commission on SDH (Solar & Irwin, 2010). In that framework, the WHO introduced two new factors - healthcare governance and government policies as inequity determinants. All the factors were divided into two sets of determinants – Structural and Intermediary.

2.5. Systems-Thinking Approach

WHO very effectively explained health system building blocks in their flagship report published in 2007 (WHO, 2007). Still, a gap of understanding exists between system definition and system behaviour. All health system building blocks are related and interconnected with each other. A small change in any one of the factors gets reflected in others too. Some basic characteristics can be observed in every system and health systems are also not different from them. Most systems are constantly changing, tightly linked, and self-organizing. Efficient and effective intervention design will not be possible until relationships among factors get identified. In several other domains of engineering, the *systems-thinking* approach has been applied for measuring underlying characteristics of the system.

MCH systems were usually conceptualized as monolithic systems. System-wide interactions among its components were seldom got scrutinized by researchers. MCH is a very complex system. There are different types of interventions such as adolescent interventions, antenatal interventions, postnatal interventions, infant and childhood interventions, and different layers in delivery care such as community care, outreach patient care, clinical care, etc. Along with coverage improvement, healthcare service inequity reduction among different socio-economic population groups is also a great challenge.

Till now for improvement of MCH condition, maximum interventions were designed and evaluated based on their effects on single or couple of health system blocks (Yuan et al., 2014). The systems thinking approach proposes system-wide knowledge generation for efficient intervention design. It not only concentrates on the outcome but also helps to identify linkages, interactions, behaviours, and relationships among all the elements included in the system (De Savigny & Adam, 2009). The paradigm shift is required in thinking patterns for MCH research. Previously health systems were considered static and external interventions driven. Concepts of detailing and single factor research were predominant. There was no concept of within system relationship and behaviours analysis.

Advanced computational techniques can be applied to unveil the underlying relationships among MCH related factors. One of the effective techniques such as data mining techniques can be applied for system-wide knowledge generation. Data mining techniques are also known as knowledge-discovery techniques. Aim of these techniques is primarily extracting a pattern from raw data that can be utilized for decision making. These kinds of evidence-based decision-making processes were used in different disciplines. Identifying suitable data mining techniques for problem analysis is a tough job for non-experts. For the benefit of healthcare decision-makers, an automated data mining system, also known as knowledge-discovery based DSS, has been proposed in this article. This interactive system would help to identify relationships among different agents present in the maternal and child healthcare system of any region.

3. Decision Support Systems (DSS)

DSSs help decision-makers in problem-solving – simple or complex, semi-structured, or unstructured. The concept of DSS was created by Gorry and

Scott-Morton (Gorry & Scott-Morton, 1971). The concept of structuredness in the decision was first described by Simon (Simon, 1977). He has classified decisions into three types – *structured*, *semi-structured*, and *unstructured*. Structured decisions are repetitive by nature and unstructured decisions are fuzzy and complex types. Anthony (Anthony, 1965) categorized all types of management control activities under three classes. Those were *strategic planning*, *management control*, and *operational control*. Gorry & Scott Morton have merged the above two concepts and proposed a 3 by 3 matrix as a decision support framework. It has been realized by them that activities with the unstructured and semi-structured decision could not be handled with existing conventional management information systems. In those cases, human interventions are required for efficient decision making. The concept of DSS has evolved where decision-makers and computer techniques collaborate to solve complex unstructured and semi-structured problems.

In the beginning, DSS has come up with three basic sub-components – database management system, model management system, and graphical user interface. A database management system is used for storing and retrieving data. A model management system is used for analyzing data and preparing alternatives and users became interactive through graphical user interfaces. As the technology evolved, usability and efficiency of DSS both have also improved. Many pieces of research have worked for the improvement of decision making quality of systems. The invention of Internet technology and the development of Web-based DSS made group decision making possible and easy. The Internet has helped to disseminate information to all geographically distributed decision-makers at a time. It has increased demand for Web-based DSS.

For having the advanced computational capability, the applicability of knowledge-driven DSS has spread over several domains. In this system, different data mining techniques are applied to data to discover knowledge from them. There are four major types of data mining techniques. These are *association*, *prediction*, *clustering*, and *visualization, and sequential relationship*.

The Association rule mining technique is used to exhibit relationships among the variables within a large dataset. In the retail industry, this technique has gained much popularity. Now other domains are also using this algorithm for knowledge generation. As the name suggests, the prediction is related to future forecasting. In data mining, the prediction technique is used to develop a quantified model through which some variables or indicators can be predicted. Based on the nature of the predicted variable or outcome variable, the prediction technique has been classified into two broad categories – classification and regression techniques. If the outcome variable is numerical data then the regression technique is applied otherwise the classification technique is used. The clustering technique is used to segment large dataset into groups with similar kinds of data. Another major data mining category is visualization and time series relationship. Visualization can be used alone or with other data mining techniques to comprehend the dynamics among different factors. Time-series or sequential relationship is a special kind of predictive model where historical time-series data are analyzed for future prediction.

There are many examples of the application of data mining techniques in healthcare. All works can be broadly classified under few categories – evaluation of treatment effectiveness; management of healthcare; fraud detection in healthcare insurance; etc. (Koh & Tan, 2005). But examples of knowledge discovery based DSS in the healthcare management segment is lacking. Very less number of research literature has been found out by searching for different databases.

There are many advantages to integrating both data mining techniques and DSS. Data mining techniques help to extract a different kind of information or pattern from data but according to the nature of the problem, decision-makers need to choose specific data mining technique among all and apply it properly by arranging data efficiently. DSS can help decision-makers to store all important variables efficiently in one place and then arrange them effectively according to the need of the algorithm. Efficient synchronization among both data mining techniques and DSSs has helped to solve many problems from several domains (Delen et al., 2007; Zeng et al., 2012). In the primary healthcare management segment, evidence of this kind of work is very rare. One project, called MediMap has been observed for public healthcare resource management at Slovenia (Lavrač et al., 2007).

4. The Proposed Design of the DSS

In this work, a DSS has been developed for understanding the MCH system much more elaborately. This system will help healthcare managers, especial-

ly from developing countries for designing efficient interventions where resources are a big constraint. Keeping systems thinking approach in mind, different modules have been prepared for measuring the dynamics of health system building blocks with each other. There are two major components of the system – the database component, and knowledge discovery modules. These two subsystems have been discussed further elaborately.

The generalized architecture of a DSS has been portrayed in Figure 1. Users utilize Graphical User Interface (GUI) for interacting with the system. All data are stored under the database management system which can be accessed by users through the interface. Data are analysed through different kind of techniques, stored under the model management system to extract knowledge from them. Users can choose models according to problems. Discovered knowledge is used by the user for evidence-based decision making and also gets stored for future usage.

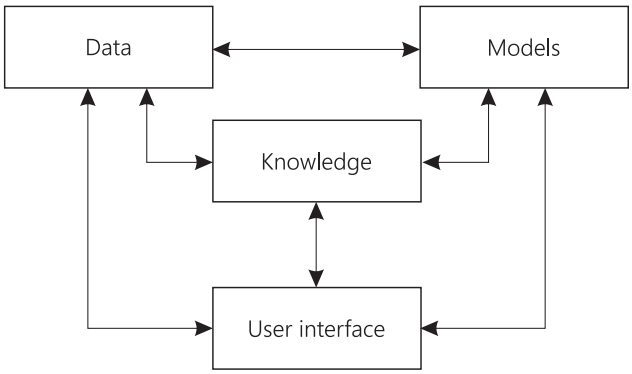

Figure 1. High-Level Architecture of Decision Support System

4.1. The Database component

Data for the system have been categorized under four major segments. These are MCH indicators; ESE parameters; healthcare interventions; and health system building blocks.

4.2. The Knowledge discovery modules

This is the core area of the system where statistics and data mining techniques are used for knowledge discovery. As discussed previously, there are four major data mining techniques – *association*, *classification*, *clustering*, and *visualization techniques*. Three major knowledge-discovery modules have been developed by using all four techniques. Details of modules and sub-modules under each module have been portrayed in Table no. 1.

Table 1
Details of System Modules

Module	Sub-module	Variables	Technique Used	Knowledge Extracted
1	I.	Maternal and Child Healthcare Indicators Educational, Social, and Economic Parameters Maternal and Child Healthcare Interventions	Visualization	Coverage of healthcare interventions throughout different socio-economic strata and their effects on healthcare indicators
1	II.	Maternal and Child Healthcare Indicators Educational, Social, and Economic Parameters Health System Building Blocks	Visualization	Availability of health system factors throughout different socio economic strata and their effects on healthcare indicators
1	III.	Educational, Social, and Economic Parameters Maternal and Child Healthcare Interventions Health System Building Blocks	Visualization	Relationship among interventions and health system blocks throughout the different socio-economic condition
2	I.	Educational, Social, and Economic Parameters	Clustering	Segmentation of regions based on their social, economical, physical, and educational conditions.
2	II.	Dependent Variables: Maternal and Child Healthcare Indicators (Segment-wise data) Independent Variables: Maternal and Child Healthcare Interventions (Segment-wise data)	Classification and Regression Technique	Impact of maternal and child healthcare interventions on healthcare indicators for each segment.
3	I.	Key Influential Maternal and Child Healthcare Interventions Segment-wise Health System Building Blocks	Association Rule Mining	Internal dynamics among healthcare interventions and health system building blocks

4.3. The Software Platform

After analyzing different software platforms, R statistical software platform has been finalized. The DSS has been prepared by using Shiny package on R software (Wojciechowski et al., 2015). Shiny package helped to incorporate data mining algorithms with the DSS and publish the system on the Internet.

5. Results & Discussions

The first module has been prepared by using the statistics and visualization technique. In this module, a three-dimensional scatter plot has been developed for visualizing relationships among variables. Three sub-modules have been prepared. In the first sub-module, coverage of healthcare interventions throughout different socio-economic strata and their effects on healthcare indicators can be visualized. The second sub-module shows the availability of health system factors throughout different socio-economic strata and their impacts on healthcare indicators. The relationship between healthcare interventions and health system blocks throughout different socio-economic conditions can be viewed in the third sub-module.

The first sub-module of the second module has been developed for the segregation of regions based on MCH conditions. MCH outcome of a region depends on the coverage of priority interventions (Countdown 2008 Equity Analysis Group, 2008; Victora, Barroa, et al., 2012) and coverage of interventions depends on the socio-economic condition of a region (Balarajan et al., 2011). In this research work, 284 districts from nine states of India have been segmented based on their socio-economic conditions for checking the efficiency of the module. The hierarchical clustering technique has been used for the segmentation task. Statistical test ANOVA has been conducted to prove that segments were significantly different from each other. It has been observed that majority districts of Bihar (94.6 per cent), Jharkhand (66.67 per cent), and Uttar Pradesh (58.58 per cent) have been included under segment one. Segment two was developed by a collection of districts from Assam (82.60 per cent) and Uttarakhand (84.61 per cent) whereas majority districts of Chhattisgarh (75 per cent), Madhya Pradesh (75.55 per cent), and Rajasthan (53.12 per cent) have been clustered under segment three. 60 per cent districts of Odisha reside under segment one and 36.66 per cent clustered under segment three. Average values of ESE parameters have been computed to understand the socio-economic conditions of each segment. The average literacy rates of both males and females were higher at districts under segment two and lowest at districts under segment one. The availability of basic infrastructural facilities was also much higher at segment two with respect to other segments. As per the result, the average percentage of households that had electricity connection at districts under segment one was only 26.39 per cent whereas the same was 65.96 per cent at districts under segment two. MCH conditions of each segment have been analysed by calculating the average values of both MCH indicators and coverage rates of MCH interventions separately for each segment. After reviewing results it was clear that districts under segment two were the best performing MCH healthcare districts whereas districts under segment one were the worst performing MCH districts. The developed module has properly segmented all 284 districts into good performing, moderate performing, and poor performing clusters by segregating them based on their socio-economic conditions. Average U5MR at districts under segment one was 87.54 per 1000 live births whereas the same at districts under segment two was 67.94. A similar situation has been observed with IMR and MMR too. Coverage of MCH interventions have also been computed and compared among all three segments. The coverage of the majority of MCH interventions was comparatively lower at districts under segment one with respect to other segments.

The second sub-module of the DSS has been prepared for the identification of MCH interventions which had high impacts on MCH indicators separately for each segmented region prepared in the previous sub-module. In this work, the decision tree technique has been used for classification. Nine classification models have been prepared separately by classifying all MCH interventions against IMR, MMR, and U5MR values for all the three segments prepared in the previous module. By applying healthcare data, it has been observed that adolescent healthcare interventions and childhood healthcare interventions were key influential interventions for all MCH indicators in all three segments (Saha, 2019).

The third module is for finding out all frequently occurring healthcare service elements and their availability conditions when coverage of key influential MCH intervention, found out in the second module, was either poor or moderate or good at any region. In this re-

search work, the association rule mining technique has been used instead of preparing causal loop diagrams for generating system-level knowledge about health system building blocks. After analysis, it has been observed that community healthcare services, SC level services, and PHC level services are very much interlinked with each other. Few particular sets of variables have frequently occurred together for making a region either good performing MCH region, moderate performing MCH region, or poor performing MCH region. By reviewing all results it has been observed that availability of village-level health and sanitation committee (HSNC), Rogi Kalyan Samity (RKS), and Panchayat Raj Institution (PRI) was comparatively higher at good performing MCH regions and availability of all these village-level healthcare committees was very less at poor-performing MCH regions. Another factor has been observed that the influence of ASHA workers on adolescent and pregnant women for utilizing antenatal care, family planning techniques was very less at good performing MCH regions. The major reason for less influence was higher awareness of healthcare services among females in those regions. The influence of ASHA workers was very less at moderate performing regions too. The influence of ASHA workers can be utilized as an indicator of the healthcare condition of any region. Among SC level services; few services have frequently occurred along with these adolescent interventions at good performing MCH regions. Availability of male healthcare workers at SCs, availability of auto disposable syringe, IFA tablets, and ORS at SCs, communication facility at SCs, and SCs located at government buildings were higher at good performing regions. At poor-performing regions, the important factor noticed was the lack of availability of funding for SCs. Due to a lack of funding at SCs, the availability of basic essential drugs and skilled health workers were very less in those areas. In the majority of poor performing MCH districts, availability of a personal computer, freezer, incubator, and normal delivery kit was quite alarming at PHCs. The scarcity of lady medical officers at PHCs was also common in those districts. On the other hand, the availability of personal computers and freezers has been observed in every PHC at good performing MCH regions. Few important patterns have also been observed in those PHCs. Every PHC had prepared a plan for that current financial year, received untied fund in the previous year, and organized training programme at respective PHCs.

By reviewing the above results, it can be inferred that the availability of services of a region starts at the PHC level and gets percolated to the community level through SCs. To improve the healthcare condition of a region, proper planning and financing at PHCs are very important because all-important medical equipment and emergency facilities are available at PHC only. The primary purpose of an SC is to provide basic drugs and skilled healthcare service personnel. All results have highlighted that at good performing MCH regions, all SCs had sufficient availability of basic drugs like ORS, IFA tablets and had skilled health workers. Results were also emphasizing that in good performing MCH regions, all PHCs did prior planning for funding and all SCs under those PHCs got a proper supply of medicine and human resource. The exact opposite scenario has been observed at poor-performing MCH regions. From results, it can also be confirmed that at good performing MCH regions, females were already educated about healthcare services. That's why the Influence of ASHA workers on pregnant or adolescent females was quite less at good performing regions. On contrary, at good performing MCH regions, availability of village-level HSNC, RKS, and PRI was quite high and results were also confirming that a well-managed PHC had a high influence on the availability of village-level healthcare committees. These results are confirming that the proposed analytical framework along with the developed DSS can be very useful for healthcare policymakers for the reduction of inequity among regions by incorporating systems thinking approach in their decision-making process.

6. Conclusion

In this paper, the design of a knowledge-based DSS has been proposed. The primary aim of this system is to help healthcare managers to develop suitable interventions by analysing all types of MCH related information. System-wide knowledge of the MCH system of any particular region will get generated through this system. All MCH related factors i.e., MCH indicators, healthcare interventions, health system factors, educational socio-economic parameters, have been included in the proposed system. There is always room for improvement. In the future, works would be required to verify the computational ability of each module. If required, new techniques would be included and compared with old algorithms for the betterment of solu-

tions. Based on the literature review and expert opinion survey, new parameters would also be included for further improvement of the system.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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The impact of rock music on Indian young adults: a qualitative study on emotions and moods

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Abstract

Music has proven to play a vital role in social and emotional development in teenagers and young adults. From contemplation, developing self-identity, understanding interpersonal relationships, and providing possibilities of experience mastery, agency, and self-control with the help of self-directed activities, music helps its audience develop in all aspects of life. In specific, Rock music, since its existence has been more than entertainment, artists expressed themselves and shared their opinions through their musical pieces. Infamous for promoting drugs and alcohol, Rock Music used its platform to enlighten the audience about taboo topics like racism, inequality, and other social issues. This research paper uses a qualitative methodology approach to understand Rock Music listeners' points of view. Data was collected through 'in-depth interviews' of 15 participants hailing from different parts of the country. Rock Music has several positive effects on the listeners. Rock can elevate moods, induce emotions, helps the listeners be more productive and creative with their everyday work, and constantly motivate them to do better in every aspect of life. Rock provides a platform to express feelings and vent out all the angst, especially for those who otherwise do not voice their opinions because of their nature in general. Rock Music has been able to shape personalities, characteristics, and thought processes. Moreover, majorly, Rock Music helps people with anger management.

Keywords

Music, Moods, Emotions, Positive effects, Rock, Mood-booster, Motivation, Anger-management

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Introduction

Rock music is a popular music genre widely celebrated amongst adolescents and young adults. Discovered in the early 50s, this genre of popular music has used its medium to talk about social and political issues [1]. However, many observers believed Rock n' Roll harmed the youth; in a sense, the music (supposedly) encouraged teenagers to rebel against the societal rules, parents, and authoritative figures, leading to experts conducting research. Most of the studies show that music, in general, impacts the individual's personality, actions, moods, decisions, and even cognitive enhancement [2].

To begin with, listening to music has reportedly proven to be an effective means of boosting mood, increasing productivity, and relaxation. Several readings show those adolescents, adults, and even the elderly population use music for mood regulation [3]. Music has proven to play a vital role in social and emotional development in teenagers and young adults. From contemplation, developing self-identity, understanding interpersonal relationships, and providing possibilities of experience mastery, agency, and self-control with the help of self-directed activities, music helps its audience develop in all aspects of life [4]. Music boosts an individual's mood and helps deal with negative emotions, uplifts the spirits, and provides them with some relaxing experience(s) [5]. Studies also suggest adults strongly connect to music, as it helps in emotional development and self-conceptual processing. A study conducted by Sloboda, O'Neil, and Ivaldi proves that music and its effect on the adult samples were closely related to moods, memories, and emotions [6]. Affect Regulation is an important concept discussed in various academic papers to understand music and its effects. According to experts, individuals make conscious decisions to listen to music to alter their moods and emotions, called Affect Regulation [7].

Rock n' Roll first emerged in Cleveland through a radio show in 1951. Alan Freed, a radio host in Cleveland, played some rock in the radio station for the listeners. According to several findings, Freed hosted Moondog Coronation Ball – the first-ever rock n'

roll concert [8]. Then comes the 1960s, the decade when Rock n' Roll thrived and became the 'pop' music. Several artists experimented with this genre and gained popularity, like Elvis Presley, Chuck Berry, Bo Diddley, Buddy Holly, and Little Richard. Rock n' Roll expanded such that, with time, it was identified as 'Rock Music' and gained major traction [9]. After a worldwide rock movement, popular bands emerged like The Beatles, Gerry, Pacemakers, Freddie and the Dreamers, Animals, and Rolling Stones. However, that is not where it stops; rock music continued to expand, the artists experimented with the popular genre and created sub-genres like Psychedelic Rock, Punk Rock, Glam Rock, Roots Rock, and Heavy Metal. Rock music has evolved throughout the years, and it is observed that today Pop Rock and Indie Rock are highly popular among the youngsters [10].

Rock music, since its existence, has been more than entertainment; artists expressed themselves and shared their opinions through their musical pieces. Infamous for promoting drugs and alcohol, Rock Music used its platform to enlighten the audience about taboo topics like racism, inequality, and other social issues [11]. Studies show Rock Music enabled freedom of speech since the 1960s in the most honest and effective form [12]. Experts believe that rock is a rebellious genre of music, projecting negative emotions, especially in youth culture; however, research conducted by scholars from the University of Queensland found that Rock Music can be a potential mood booster and improve listener's well-being, and is effective for anger management [13]. Rock music can be distinguished into two types: Hard Rock and Soft Rock. Both types serve different moods to the listeners [14]. For instance, Soft Rock regulates positive emotions and increases productivity while Hard Rock induces negative emotions [15]. Several studies suggest that Rock Music and Metal Music increase feeling, and extreme music helps individuals achieve positive emotions.

For this research paper, a qualitative methodology was adopted to understand the psychology and effects of Rock Music on emotions and moods. Data collection was done via in-depth interviews, through virtual video calls [16]. Young adults between the ages of 21 to 26 were targeted, as they have a better understanding and control over their emotions. Fifteen in-depth interviews were conducted, and the analysis was done from the data collected [17].

Literature Review

In the following literature review, music, the relation between music and emotions, listeners' perception of music, musical preferences, and rock music & its effects on listeners are discussed [18]. This paper aims to concentrate on Indian young adults and their perception of rock music, how it induces emotions and regulates their moods [19].

Music is a ubiquitous phenomenon; we listen to music every day, create music, and share experiences through music [20]. However, why does music create emotions in us? There are four different explanations: (a) Learned Associations – it means an individual's geographical and cultural environment influences their understanding of music and they connect it with emotional contacts, (b) Musical Expectations – here while listening to music has become an everyday phenomenon, an individual has musical knowledge, expectations and is now aware of statistical musical patterns, (c) Expressive Emotional Movement – every emotion that we feel also has a behavioral movement to it, for instance, when we are feeling sad, we tend to move slowly in contrast to feeling happy, that is when we are active and moving fast, (d) Activating Sounds – music has a direct influence on human's sympathetic nervous system, it creates certain kind of orientation in our body. Out of these four-pointers, the first two explanations are individual-centric, whereas the last two points made are universal-centric [21]. We may be unaware, but music plays a vital role in our lives; individuals can deeply relate to their personal experiences and emotions with music. Music represents one's lifestyle, image, and social belonging [22]. In research conducted by Anne J. Blood and Robert J. Zatorre, using Positron Emission Tomography (PET), found that subject-selected music-induced intense pleasurable feeling likes "shivers-down-the-spine" or "chills." Their result showed that music is connected to survival-related stimuli along with emotions like pleasure and reward [23].

According to studies, psychology finds it strange that each individual has a different musical preference; the phenomenon is named style/genre preference [24]. According to scientific research, music executes three essential psychological functions for the listeners: (1) improve [any] task performance (for example, while completing household chores, driving, working out, etc.), (2) stimulate intellectual curiosity (cognitive abilities), and (3) manipulate one's emotional state by

achieving the desired state of mind (mood - sad, happy, anger, etc.) [25]. As research shows, listeners use music to regulate emotions. Music has three different uses, 1) active uses: it modifies mood, (2) social uses: creates a sense of belonging by exchanging music and experiences with it, and (3) uses of music lyrics: allows individuals, especially students, to acquire information and seek moral guidance (Slides.com) [26].

Researchers found that music preferences also play a vital role; music preference groups were identified based on their factor analysis which showed that 'Intense and rebellious' is one such preference that includes rock, alternative, and heavy metal music [27]. An exploratory study was conducted to analyze the role of music listening for college students and how these preferences affect their general coping [28]. The demographic page method, short test memory of music preferences (STMOMP), and four questionnaires were used to understand the purpose of the study [29]. The results showed a significant bivariate and linear correlation between music preferences and coping. Music function, significantly and moderately associated with overall coping [30]. All the coping subscales used in the study were significantly and linearly related to music function [31]. Music listening was significantly related to music function but was not necessarily associated with overall coping. There are three major aspects of music: (1) understanding communication and perception of emotion in music, (2) understanding emotional consequences while listening to music, and finally (3) understanding music preferences and predictions [32].

There are three dynamic characteristics of music: (1) Arousal – usually a song with fast beats and intense music, (2) Valance means emotional reactions – here, there are two types of positive and negative valances. Positive valance portrays happy music, negative valance represents sad music, and (3) Depth – it is how we understand the complexity of songs. In their paper, Bowling, D. L., Sundararajan, J., Han, S., and Purves, D' Expression of Emotion in Eastern and Western Music Mirrors Vocalization', explain that music and speech both denote emotions such as anger, fear, and happiness are termed as high-arousal emotions, faster beats usually portray them compared to low-arousal emotions like sadness, love or tenderness [33].

Under the semiotic approach in music, it is essential to understand music anthropology. Alan P. Merriam defines the study of music in culture linked to mutual interactions of sound, behavior, and concepts as ethnomusicology. In the early 70s music was studied and analyzed as an important sign/artifact of culture. Since then, the semiotic approach claims musical structures are denoted as affective meanings [34].

It is essential to understand emotional contagion to connect music and emotions. It is best described as when an individual "automatically mimic and synchronize facial expressions, vocalizations, postures, and movements with those of another person and, consequently, to converge emotionally [35]." The theory implies a minimum level of self-consciousness; the emotion is instantly felt. When an individual listens to music alone, he or she is most likely to respond through intense emotions; meanwhile, if one listens to music with a close friend, the response is more positive [36]. Music listeners relatively have a common emotional response to music in the form of chills, shivers, and piloerection. Music preferences are linked to emotional benefits. For example, if an individual is exposed to an anxious environment, his/her preferred genre of music will reduce their anxiety levels and provide comfort than listening to an unknown piece of music. Saam Trivedi, the music philosopher, believes music moves us because it provokes our fantasy to make conceptions. He also claimed music does not represent humans; rather, it represents the emotional expression [37]. The resemblance between musical beats and the sound we are familiar with daily drives a fantasy in our subconscious minds. Familiarity is considered one of the reasons for affective responses to music; it most likely induces emotional feelings. According to theoretical findings, speech and music share few common acoustic features, such that emotionally expressive cues, be it in the form of music or speech, remain the same in the minds of human beings [38].

When we talk about music and its relation to emotions, two positions can be defined: cognitivist position and the other is an emotivist position. While emotivist position claims, music can induce emotion so that listeners can feel the emotions, not just recognize it in the song(s). However, the cognitivist position argues, music only expresses emotions; it cannot induce emotions in listeners. Some studies show that music improves cognitive performances and academic achievements as well. While few authors argue that music does not necessarily regulate or induce emotions, individuals react to music concerning the environment; for instance, one would get angry if the

neighbor is playing loud music. Although, there have been several studies that prove that music induces certain emotions and regulates one's mood [39].

Uses and Gratifications Theory talks about two important aspects: (1) media users are active, and (2) media users are aware of their choices and consumption content. Considering the Uses and Gratifications Theory in consuming music, we can understand that individuals listen to music only to gratify their mood and probably enhance their well-being. Music helps people escape the reality of life and supports them through difficult times [40].

Through Rock n' Roll musicians in the 1960s, it is believed that their opinions and perspectives about society. Playing Rock Music was not all about having fun, but the lyrics talked about taboo topics like drugs, racism, and inequality. Precisely Rock n' Roll enabled freedom of speech for several musicians and enlightened the audience. Rock Music represents more than 'pop culture; it is a fine art and aesthetics of Romanticism. Elvis Presley and Chuck Berry represented the youth in the 1950s; they were the prominent superstars of Rock n' Roll [41].

Music is such that it encompasses several genres under it, right from classical music to rock music to jazz to pop, etc. Certain genres are visibly different, while few genres sound very similar but have distinct differences. However, any music genre cannot be defined by operational definition; the auditory sensory system can only explain it [42].

Rock Music has evolved throughout the years; it has several sub-genres under the umbrella. Soft Rock and Hard Rock, although fall under the same genre, have distinct features and characteristics, both the sub-genres generate a different kind of emotions and feelings in an individual. A study was conducted using projective and objective tests to analyze the type of emotions both Hard and Soft Rock regulate; it was found that subjects exposed to soft rock reported positive emotions; meanwhile, participants exposed to hard rock reported negative emotions [43].

Different music genres have different effects on our moods. For instance, Classical music and lyric-less music induces positive emotions, increases your concentration, and fuels a positive attitude towards everything in life. Meanwhile, Rock Music is considered to be rebellious music, which induces negative emotions, although a study by the University of Queensland found that Rock music has a positive impact and can be effective for anger management and improve the listener's well-being [44].

Despite the criticism, Rock Music continues to be a favorite to those who understand genuine and deep content. Another study from the University of Queensland in Brisbane reveals that loud and hard-hitting music helps the listeners with anger management and induces energy and active feeling [45].

If one had to imagine a Rock fan or musician, it is always in a long t-shirt, torn jeans, long hair, satanic necklace, leather jackets, and pierced belly. Parents believe rock is all about the 'rebellious nature. However, it is argued that, through rock music, the artists address social issues and taboo-like topics, which helps spread awareness and induces positive emotions towards all the community. For instance, Bob Marley's "Buffalo soldiers in the heart of America" raised a voice against American imperialism [46].

Rock n' Roll is an amalgamation of two music styles, Blues and Country. The combination of urban blues and country blues led to the innovation of Rock n' Roll. Chuck Berry, the country blues player, joined Sir John's trio and created a genre called Rockabilly. Back in the time, Chuck Berry was considered one of the first Rock n' Roll musicians (FUNK) [47].

Rock and Heavy Metal Music use the fundamental feelings end experiences to serve the society with some relatable content and entertainment. However, few people believe Rock and Metal genre is devil's music, to argue that a longitudinal study shows individuals who grew up in the 80s & 90s era are leading a healthy and successful life. So, even after listening to "devil's music," the kids from 80s & 90s turned out fine. Researchers have found that people who are more aggressive and violent can achieve positive emotions through metal music. It is because metal music has increased arousal feelings, and at the moment, it matches the person's physiological state. Few studies also reveal that listening to extreme music can help individuals' process anger. A detailed study on 414 British undergraduate students reveals that participants who like metal music were open to experiences, unique, and hated the authority.

Research Questions

1. Why do people prefer listening to Rock Music?
2. Does Rock music have positive effects?
3. Can Rock Music induce emotions and regulate moods?
4. Has Rock Music shaped personality (ies)?

Research Method

This research paper uses a qualitative methodology approach to understand Rock Music listeners' points of view. The qualitative methodology aims at understanding subjective answers, personal experiences, and participants' perspectives about the concerned topic. The data collected with the help of qualitative methods are not 'factual data or information that can be measured. Several techniques under qualitative methodologies, like small-group discussions, semi-structured interviews, and in-depth interviews, can be used for data collection. For this paper, the researcher aims to understand emotions and moods involved while listening to Rock Music; hence, 'in-depth interviews' were taken to interpret personal experiences. As per the requirement, efforts were made to carry out a discourse analysis. With the help of discourse analysis, one can analyze spoken words in a certain social context. Since the in-depth interview method was the key approach to collect data in this paper, discourse analysis was the best way to go. Under this, an in-depth questionnaire was designed, consisting of 14 open-ended questions, and a few follow-up questions were asked according to answers given by the participants. Apart from primary data collection, as a part of the literature review, the researcher managed to find content and important theories relevant to the research topic. Data collection (including both primary and secondary data) took place in the span of four months, from May 2020 to August 2020. The sample size of the study was 15 participants hailing from different parts of the country – India. Gender roles were not taken into consideration as they did not match the objectives of the research paper. Out of the 15 participants, nine were male, and six were female, all between the age groups of 21 to 26.

Findings and Analysis

After reading through each of the interviews, several positive effects of listening to rock music were found. For instance, participants preferred listening to certain sub-genres under a rock, like Blues Rock, Hard Rock, Psychedelic Rock, Alternative Rock, Progressive Rock, Pop Rock, Punk Rock, etc., according to their moods, social context, and the activity (ies) they are performing at the very moment. Activities like exercising, yoga, working, completing an assignment, cutting vegetables, and taking a shower. Most of the participants said Rock Music could amplify their emotions, improve their moods, and induce immense energy in them. Through the in-depth interviews, it was also found that rock can increase efficiency, productivity, and creativity while working. For example, one of the participants said she prefers listening to hard rock while designing a poster or editing a video; it boosts her energy and helps her get more creative, while another participant said he prefers listening to psychedelic rock while working, it helps him focus on his work far better than not listening to any music. However, few participants do not prefer listening to rock while working on assignments or projects to meet a deadline, as the lyrics and fast beats can be distracting. So, rock does not always help in focusing on work. Anger management is another important finding in the data collected; some experts believe that hard rock can be a great source of venting out anger, which helps the listeners calm down and control their anger. One of the study participants said that rock has majorly helped with her anxiety, hyperactivity, and anger. She said, listening to rock music has immensely helped her calm down and control her emotions, and it gives her the space to think and then react. The process of venting out angst via head banging to hard rock or metal music is a popular choice amongst young adults to deal with a bad mood. It has been noticed, rock addresses several social agendas talks about taboo topics, it is a platform for the musicians to express their perspective of society, and they do so. However, even the listeners (the listeners) in this study feel rock songs help them express their feelings, voice their opinions, and boost their confidence.

Meanwhile, rock also provides different perspectives to the listeners; it helps them gauge the reality of this world and humans. Through the interviews, it was found that rock induces emotions in the participants even when they feel absolutely nothing. 14 out of 15 participants said Rock Music induces emotions that did not exist at the moment. Meanwhile, rock can regulate listeners' moods. For example, one of the participants prefers listening to Queen (rock band) when she is upset; it makes her feel better instantly; she believes rock is an absolute mood-booster. One of the most common findings from the data was 'feeling less lonely' while listening to Rock Music. Most of the participants said, listening to rock like having great company, which helps them get through the hardest times. Three participants from the study said Rock Music 'saved' them.

One understood the meaning of life; to one, rock helped her get through a rough phase, and the third person said rock helped him get over his addictions and gave him a positive direction. In simple terms, Rock Music was their coping mechanism when they were going through a hard time. It gave them the confidence to be themselves. Rock has also helped people with introspection and encouraged them to be more reflective in life. Out of the 15 samples, 13 said rock has shaped their personality, thought process, and key characteristics. It has provided a wider spectrum of life. All the participants agreed upon one common aspect that is 'social circles'; rock helped create the right social circle with like-minded people; through the music they found friends and a safe space. One of the participants said, listening to rock with friends has always been a great experience; it brings a small group of people together and ignites oneness. Through the data collection process, it was found that certain appealing elements of rock instantly draw the listeners; they were lyrics, the complexity of rock songs, and the convergence of various instruments, emotions conveyed by the artists, guitar solos, and drum beats. Common Attributes after data collection are observed in Table 1.

Table 1

Few common attributes observed after data collection

Preferred Sub-Genres Under Rock	Activities During which Participants Listen to Rock	Appealing Elements of Rock
Hard Rock	Working Out/ Yoga	Lyrics
Alternative Rock	Working on Assignments Or Projects	Convergence of Instruments
Progressive Rock	While Taking A Shower	Artists Emotions
Psychedellic Rock	While Doing Household Chores	Guitar Solos
Blues Rock	Hanging Out with Friends	Rhythm/Beat/The Music

Understanding the difference between emotions and moods, "Emotions are caused by specific events localized in time, whereas moods build up as a consequence of either a concatenation of minor incidents, persistent conditions in the environment, and/or internal metabolic or cognitive processes." It is essential to understand the difference, as most of the participants listened (and listen) to rock depending upon their moods and emotions. Firstly, popular sub-genres under Rock were Hard, Alternative, Progressive, Psychedelic, and Blues Rock. For better understanding, below is a table where each sub-genre is linked to a mood or emotions. Participants' responses do the deduction. Rock, Emotions, and Moods were created through Sub Genres, which is shown in Table 2.

Table 2

Sub-genres of rock and emotions and moods created

Sub – Genre	Emotions	Moods
Hard Rock	Happiness, Sadness, Anger	Gloomy
Alternative Rock	Happiness	Hopeful
Progressive Rock	Loneliness	Reflective
Psychedelic Rock	Sadness	Calm and Peaceful
Blues Rock	Sadness, Loneliness	Reflective, Calm, and Peaceful

Hard Rock bands make meaningful music. One can easily connect to the message behind the song more than the artist's approach (the kind of instruments used). The sub-text in the song is more impactful than the music itself. While listening to hard rock, a few of the participants calm down and introspect the situation. Few people believe hard rock makes a person anxious and maybe even induces negative emotions. However, it has been the opposite for most rock lovers. Through personal experiences and perspectives, hard rock has helped people with anger management. The main understanding here is that listening to hard rock amplifies the feeling of happiness.

After interviewing 15 young adults aging between 21 and 26, there was one common finding, all of them preferred listening to rock while performing certain activities. The most common activities were working out while taking a shower, doing household chores, hanging out with friends, and working on assignments or projects. Here, the deduction made was that listening Rock helped the participants be more efficient, get into a better mood, and increased their concentration. The following table demonstrates the emotions and moods felt while performing the tasks and listening to rock music. Emotions and Moods created while listening to rock and activities being done are shown through Table 3.

Table 3

Emotions and moods created while doing activities and listening to rock

Activities during which Participants Listen to Rock	Emotions	Moods
Working Out/ Yoga	-	Calm and Peaceful
While Taking a Shower	Happiness	-
Household Chores	-	Cheerful
Hanging Out with Friends	Happiness	Light-Hearted, Cheerful
Working on Assignments/ Project	-	Reflective, Serious

Another common emerging theme from these interviews was the appealing element(s) of rock. Although every participant in this study is a rock lover, few rock elements instantly drew them to the genre. The most common and popular choices were lyrics, the convergence of instruments, emotions portrayed by the artists, guitar solo riffs, and the rhythm/music/beats. The participants who said artist's emotions said artists express themselves through the songs. The song initially recorded in the studio is heavily experimented on and edited to make it a perfect rock song, but the same cannot be done on a live stage. The artist's live versions of the same songs are better than the studio version because he can see what the artist feels while playing and singing the track. Not only one gets to see the artist in their element on the live stage, but also, they feel it with them; a sense of familiarity is induced instantly. One of the participants said, "Music is speech. It is how one speaks but with a different language, and in this case, it is music." Live rock shows can induce the emotion which artists themselves are feeling.

Meanwhile, few samples talked about guitar and drums being the appealing elements as the vocalists can use words to express themselves and convey a message, guitarists and drummers only use their respective instruments to speak to the audience communicating, and people instantly relate to it. In this case, the amalgamation of guitar and drums enhances the songs. The sound of the drums instantly draws individuals to rock music. Drums are the backbone of any rock song, and the whole track is built upon drum beats. For example, 'Smells like Teen Spirits' by Nirvana is one of the songs that starts with the drum beats, and it instantly draws the listeners to the song; it sets the mood. Here we can notice how just the beats of the drums speak so much to the listeners; it has captivating power.

Conclusion

Music has always been a source of entertainment. Usually, people listen to music in their leisure time for stress release. Through this paper, we found that music plays a vital role in the lives of the samples who participated in this study. It is a mood-booster; it can comfort people in their dark times. Talking about Rock Music, as it is the main theme of this paper, several positive effects were found through data collection and data analysis. Rock can elevate moods, induce emotions, help the listeners be more productive and creative with their everyday work, and constantly motivate them to do better in every aspect of life. Rock provides a platform to express feelings and vent out all the angst, especially for those who otherwise do not voice their opinions because of their nature in general. The participants in the study resonated with Rock music, as it provides entertainment and educates them about the world, the naked reality, and society. Rock addresses several social agendas and talks about taboo topics, which other genres fail to cover. We found that Rock Music has been able to shape personalities, characteristics, and thought processes. Moreover, majorly, Rock Music helps people with anger management.

Limitations and Future Scope

Since the paper was directed at understanding the psychology of the listeners, the qualitative method was the approach to the study; however, 15 samples do not represent the whole of India's young adult population. One could further extend the age group and sample size. Another limitation was the medium of data collection; I had to resort to virtual interviews due to the unprecedented times. The social environment of the sample is equally important while answering questions, which was a major issue as few participants were conscious while responding to the interview questions. Apart from that, there were internet glitches as well. If one wishes to dig deeper into this topic, focus group discussions can also be another method of data collection, as it can help the researcher to understand the psyche of the samples.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Conflict situation in a suburban hospital, India: Reasons and measures to minimize

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Abstract

Health care has a prominent place in society and as a setting required to serve and care for its public and stimulate overall physical, psychological, and social health. It has a distinct obligation to generate a healthy workplace. Conflict and diversity are intrinsic in health care, and conflict in interdisciplinary teams is an accepted norm and unescapable. Thus, a study was conducted to understand reasons for the conflict amongst varied levels of healthcare staff in a 150 bedded multispecialty hospital in an Indian city. A Survey of 200 respondents (Healthcare and managerial staff) revealed that lack of appreciation, job stress, and competition within the department (32%) were the major reasons for differences amongst the employees. Concerning approaches adopted, compromising and collaborating methods scored more (38% and 38.6%, respectively). The results have shown that, in general, managers are familiar with conflict resolution techniques and believe in motivating their staff to increase their levels of performance and retain them with the hospital. However, there is a need to make the human resource system more robust and accommodating to ensure varied healthcare professionals from different qualification backgrounds and job roles are treated equitably

Keywords

Conflict, Hospital, Healthcare, Resolution, Staff, Qualification, Stress, Competition

Imprint

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Introduction

Healthcare is distinctive in numerous ways. On the other hand, it is comparable to other organizations in how individuals conduct themselves, and this is where conflict comes in, where it is one of the most common issues faced by healthcare team members. [1] There are numeral features of the healthcare system that helps to create misunderstandings and differences. These disputes give rise to many conflicting situations.[2] Often, conflicts are inevitable, and given the charged-up nature of activities that go inside any healthcare setup, these instances have been and will arise often. Additionally, the stress element, which is inherent when it is a matter of saving lives everyone, has their own opinions and points to put forward. With many people around, avoiding indifference is not possible.

A healthcare team comprises doctors, nurses, paramedics, administrators, biomedical engineers, dieticians, physiotherapists, and many other as per the need of the patient and as per the specialty services offered by the organization. [3] These members form a very diverse group. This group interacts with the patient and his/her family and friends. This interaction also, at times, leads to disparity on a couple of things resulting in conflict. In many organizations, conflict is being cited as the reason for high employee turnover.

Although any reason is good enough to initiate such negative encounters, major sources that lead to conflicting situations include- personality differences- this center around dissimilarities observed around team members' attitudes, [4] principles, cultural background, education, emotional wellbeing. Other being not agreeing based on ethical or moral considerations. Discrepancies with professional job roles and responsibilities. Common resources and improper distribution of the same. Constrained decision-making process as lead consultants of the healthcare team still take many decisions. [5] Apart from these, many studies have pointed out that the single most reason for conflict is miscommunication or no communication amongst the team members, like the use of harsh words, language, believing in rumors, criticism, etc., are part of communication that can offend many in the system. Further gender diversity, performance-related issues, financial restraints are other reasons leading to conflict.

Inside healthcare, misinterpretations, and conflict typically comprise several different parties and occur at several levels. [6] The healthcare system involves the extensive inconsistency about knowledge, control, and influence experienced by its many performers. The ethnic diversity at the workplace, too, can lead to the building up of possible hurdles to helping parties come up with the solutions.[7] Hospitals usually have a tight hierarchical structure formed based on specialization and qualifications; this again leads to conflicts amongst the various levels in an organizational structure.[8] Failure to address these persistent encounters can lead to health errors, staff exhaustion, and many medico-legal issues. As health care highly depends on unified linkages of multiple players, thus making it more important to have a very cordial relationship amongst each other.

There cannot be any workplace where an ideal conflict-free environment exists. While a sensible extent of disagreement in the form of competition sometimes leads to a greater level of performance.[9] Conflict inside any workplace is a predictable and unavoidable event and negatively affects both individuals and at an organizational level unless appropriately managed. This result in manager is spending their precious time in settling the issues. It has been perceived that most executives devote roughly around 25% of their time dealing with conflict-related issues and their settlement. In hospital administration, this time can be as much as 50% given the various types of human resources involved.[10] Thus, conflict resolution in hospitals is as important as any other managerial function like planning, organizing, directing, etc. [11] Further, another study states that conflict distracts from immediate tasks and wastes resources on conflict resolution. Although helpful, it is clear that several occurrences of conflict are risky and impact smooth conduct of activities.

But conflict is not all a negative thing. There are proposed benefits too, as highlighted by researchers in other studies. They include a better understanding of the task, team development, and enhanced quality of group decision-making.

Probability of conflict increases in healthcare organizations when rules and regulations are not followed, and instructions are ignored. [12] Especially in the hospital where many activities are followed as per the protocols, and standard operating procedures, unfollowing them is a huge issue leading to chaos, confusion, and conflict.

Healthcare professionals face conflict situations almost every week. The number may vary depending on high-stress job factors, team size, management functioning, and others.

As a result, it is significant for healthcare experts and administrators/ managerial executives to comprehend the origins of conflict and improve approaches to accomplish the settlement. [13] Accordingly, with this background, a study was conducted to explore the diversity of roles and responsibilities of the employees and their perspective towards the tasks assigned, group work, their professional values and morals, and the way the hospital treats them for the work done. Thereby analyze how conflicts manifest in different dimensions at the hospital.

This descriptive study was conducted with the following objectives:

- Examining a variety of different perspectives of the employees and the managers and identifying underlying work stress, disputes, and dilemmas
- To find the source of conflicts
- To understand approaches used to mitigate the conflicting situation.
- To suggest certain measures to overcome the issues leading to conflicts and improve the hospital's working environment.

Materials and methodology

This study was conducted at a 200 bedded super specialty hospital in Bengaluru, a metro city in the South of India, for one month.[14] The management of the hospital initiated the study to understand the current situation prevailing in their setup related to the conflict.

An informal interaction was done with the employees and managers at the hospital to understand their perspective. A structured questionnaire was designed and distributed to 200 employees, including medical, paramedical, and managerial staff. An informal interaction followed this to collect data from the participants. [15] The participants were informed about the type and objective behind the collection of the data. The instrument developed consisted of questions pertaining to employment, level of job position, the expanse of job role, issues encountered, and reasons for conflict situations and approaches to minimize was asked to the respondents. The content was approved and validated by senior hospital staff before its implementation.

Responses were collected by interviewer-based survey. This ensured a 100 percent response rate and avoided the chances of incomplete survey forms.[16] Data entry and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 23. The data are presented using descriptive statistics in the form of frequencies and percentages for the qualitative variables.

Results

Interdepartmental and intragroup conflicts are the most common source for conflict situations at the hospital. This was a simple study to understand why conflicts occur and an approach to minimize, inferential statistics were not performed.

Out of 200 respondents, 53.6 % were male, and 46.4% were female employees. These employees belonged to the mean age group of 31-40 years, having work experience of an average of 8 years and above. 36% of employees were working on a contractual basis whereas 64% were permanent employees. It was important to understand the hospital employee mix and the various job roles and hierarchical patterns that lead to conflict. Figure 1 depicts the employee mix of 200 responders.

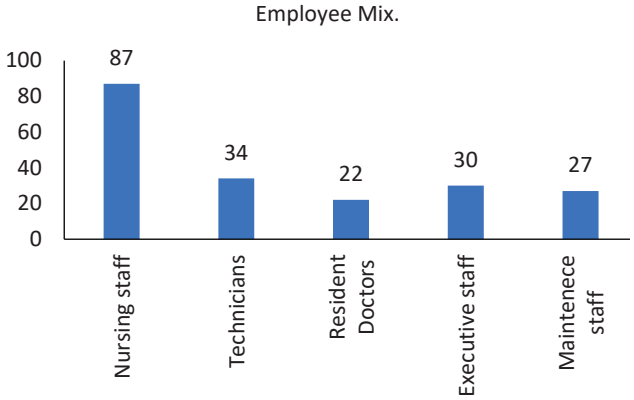

Figure 1. Employee mix in numbers.

The employee distribution has 43.5 % nursing staff, which forms the largest proportion, followed by technicians at 17%, managerial staff (also referred to as executive staff in hospital) forms 15%, maintenance staff is 13.5%, and resident doctors are 11% of the entire sample size taken for the study purpose. Depending on the employee mix, it was assessed what type of employee group attributed to the rise of conflict situations at the workplace. It was found out that conflicts were most often attributed to resident doctors (59%), followed by nurses (over 19%), technicians (10%), executive staff (8.2%), and maintenance staff (3.8%).

Health care is a multi-faceted organization that necessitates effective collaboration and cooperation within the varied teams working for patient care and delivery of services. Frequent causes of conflict include lack of clarity with expectations, improper communication, lack of clear authority, behavior differences. These are some of the main reasons why differences are created amongst the members of the same team-leading to misunderstandings and a range of disagreements. Following these major reasons for conflicts were asked to the participants, which are depicted in Figure 2.

Figure 2. Reasons of conflict

Most employees are dissatisfied with their workload, timing, and salary issues (15%). In addition,(3%) of them showed dissatisfaction and disagreement towards the leave policy and health assistance provided to them. Further, it was also noted that there is a lack of enough experienced staff and a lack of training for the new and old employees. The majority of the employees also face a lack of appreciation and opportunity to grow and develop, which adds to their job stress and dissatisfaction, resulting in competition within the same department or between departments (32%). When given a group task, they were mostly not satisfied with individual roles (6%) as some felt that menial jobs but labor-intensive are always given to nurses. At the same time, resident doctors and other executive staff do not contribute more. They are also asked to work on very limited resources, which doesn't aid in fulfilling their work requirement as it should be, resulting in many displeasure interactions with each

other, petty fights, etc. (3.2%). On the other side, few managers also show dissatisfaction towards work productivity of their employees due to which patient expectations are affected (12.9%). Communication should be transparent and comprehensive enough to develop a clear understanding for any work to be successful. If communication is not proper, it creates a lot of misunderstanding and thus giving rise to the conflicting situation, which in this case too as reported by (22.6%). However, conflict resolution is important for all the managers for which they mentioned discussing and resolving the situation and motivating their employees as much as possible by verbal appreciation.

Approaches took to resolve the conflict

It is reported that resolving and managing conflicts takes away 25 % to 40% of the time of managers and senior officials. Many studies and literature available on conflict management suggest five approaches to deal with the same. It includes:

- Accommodating: The objective of this strategy is to yield – to protect amicability and connections no matter what.
- Compromising alludes to a dealing interaction that regularly results in a not so great arrangement as concessions are made
- Collaborating: The objective is to track down a shared arrangement when the two arrangements of interests are too imperative to even think about being compromised.
- Avoiding: This strategy can be utilized deliberately, for instance, to make a defer that permits individuals to chill off or accumulate more data.
- Competing is, for the most part, a negative method to oversee struggle. The objective is to "win" no matter what, and high emphatics and low collaboration portray the style.

Since the above approaches are very commonly adopted practices in many organizations, this study also considers the same.

Depending on the above, the response is being obtained from the participants to highlight generally which approach is usually used by them for conflict management situations in the hospital. Table1 lists the approaches adopted by the responders.

That compromising and collaborating are the two most sought-after approaches with almost equal responses of (38.6%) and (38%) respectively. (11%) of the respondents felt that a most accommodating approach is adopted by seniors to settle the issue and (12%) think that in some instances, avoiding is also adopted as moderating measure. It is a good sign that none of the respondents has agreed on the competing approach being adopted. This shows that the hospital management takes care of the negative situations and resorts to adoptinging other positive approaches rather thcompetingeting amongst themselves, which may rein in a more cruel experience.

Table 1

Approaches for conflict resolution

S.No	Approaches	No. of Response (n=200)	Percentage Responses
1	Accommodating	23	11.4%
2	Compromising	76	38%
3	Collaborating	77	38.6%
4	Avoiding	24	12%
5	Competing	0	0%

Discussion

The study's findings and informal interaction have revealed that variables such as the opportunity to develop, levels of job satisfaction, job stress, ability to perform well with team and staff relations were seen to have a substantial effect on overall job satisfaction. Ignoring any kind of grievances could lead to possible conflict. This situation at any given time is not suitable as it can directly affect the patient care routine. Since the amount of human interaction is maximum in hospitals, reducing such circumstances is desirable.

Conflict arises anywhere where more than one person is involved. The causes of conflict range from rational dissimilarities and divergent goals to power inequalities, especially in medicine with varying levels of the workforce involved in inpatient care. Unmanaged or poorly managed conflicts cause an interruption in normal workflow, causing mistrust and lost efficiency. This is clear from the results where the majority of the conflicts are attributed to clinical staff than non-clinical staff. This is also because the job responsibility of clinical staff is more demanding as they are in a straight line involved with patients, their management, and it affects the outcome of treatment. Many such conditions push them into a skirmish environment.

Anaccuratesupervision of such conflicts gives an opportunity for the manager to surge the output of its

employees, thereby increasing the organizational efficiency. The results have shown that, broadly, managers are acquainted with conflict resolution methods and rely upon encouraging their staff to improve their levels of performance and retain them with the hospital. However, it is essential to make the human resource system stronger and more conducive. There are also suggestions given in many similar studies that efforts to avoid unhealthy and personal conflicts arising should be avoided.

The results also suggest that underlying factors like working conditions at the hospital are unable to meet the beliefs and ambitions of the employees on certain occasions. While the circumstances under which work is achieved can have as much influence on employee's efficiency, comfort also safety as the intricate particulars of the task itself. Since job satisfaction has a strong relationship with work performance, conflicts, and disputes, it is important to highlight relevant human resources policies, improving working conditions, to review, compensation, and motivation to improve it.

Furthermore, conflict does not remain unresolved, as when evading, there are no obvious winners at the expenditure of others. At the same time, accommodation strategies with clinicians might be suitable for the nurses if they did not feel that their goals were so significant. This sensation might be due to low self-confidence amongst few cadres of employees or a sensation that the other party of the conflict is more solid than them as the responses to approaches used in conflict resolution suggests.

From informal interaction, many of the executive staff said, "In any of the given situations of difference or disagreement, the morale and success of the organization should not be compromised." Empowering employees to make decisions about their work and a strong emphasis on the participatory approach between Clinical and Non-clinical staff should be the primary focus which management should initiate. Continuous service evaluations and monitoring of job fulfillment along with surprise audits. On-job and Off-job training and appointment of training managers and conduct of specific area related training and generic training on organizational behavior, team dynamics, developing comradeship should be part of the hospital management routine. Reducing the number of shifts and extended working hours can go a long way to bring the job-related stress factors down.

However, the study presented with few limitations as the information obtained is based upon the subjective perspective**.** Even due to the high level of contribution overall, there is an opportunity that responses of managers who did not contribute may have varied in some manner from those who did participate**.**

Conclusion

Conflicts, in general, have many downfalls affecting one's job, motivation at work, and career decisions. It also has an impact on relationships with others and personal health. Conflict management minimizes the negative outcomes of a conflict and endorses the optimistic outcomes with the goal of improving the learning and culture of the organization. People working in a job that is very challenging also sometimes changeable as healthcare can be prone to feelings of ambiguity and reduced job fulfillment. Certain the crucial role that healthcare professionals play in determining the sustainability, efficiency, and effectiveness of health care systems, it is authoritative to understand what causes conflicts, what keeps them motivated, and understanding the extent to which contextual variables and the organization satisfy them. Everyone in the system has a responsibility towards understanding the causes of conflict also ways to mitigate it for the larger good. Conflict resolution should not just be left for management. Every cadre and senior-most person in each team has an equal responsibility to establish a good working partnership to make the work environment more favorable.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Simulation model for Covid-19 pandemic

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Abstract

This paper outlines computer modeling algorithms designed to predict and forecast a COVID-19. In this paper, we consider a deterministic model. Theongoing COVID-19 epidemic quickly spread across the globe. Significant behavioural, social initiatives to limit city transport, case identification and touch tracking, quarantine, advice, and knowledge to the public, creation of detection kits, etc. and state measures were conducted to reduce the epidemic and eliminate coronavirus persistence in humans around theworld from stopping the global coronavirus outbreak. In this paper, we propose a basic SIR epidemic model to show a simulation, the MATLAB algorithm using bouncing dots to depict safe and sick people to simulate infection spread. The graphical model shown here is implemented using MATLAB package version 3.0.

In this paper, we discuss the importance of models because they help one explore what could happen. They demonstrate how different possible futures might be shaped by what we are doing now. We can examine the effects of specific interventions in different ways such as quarantine or a lockdown & explore how simulations may predict, how infectious diseases advanced to show the possible result of an outbreak, and better guide initiatives in public health regarding the pandemic response andpandemic past including an overview of the key characteristics of adverse pandemic consequences and epidemic outbreak.

Keywords

Simulation modeling, Flatten the curve, Pandemic, COVID-19, Coronavirus

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1. History

Pandemics are generally epidemic occurrences that are common due to the transmission of human-to-human contamination; the current virus has been distributed in large quantities to trigger population occurrences. Such communication among humans indicates a high risk of developing a pandemic. “The term “pandemic” originates from the Greek “pan-”, “all” + “demos,” “people or population” = “pandemos” = “all the people [1].””

A pandemic is an epidemic and infectious disease outbreak that has developed through a wide area, several continents, or across the globe, involving many citizens. Not only is a pandemic an illness or disorder if it is common or killing many people; it may even be infectious. There have been a variety of big pandemics in the modern experience.

Recent years have witnessed at least six major outbreaks. “Pulmonaryhantavirus syndrome, extreme acute respiratory (syndrome, H5N1 influenza, H1N1 influenza, Middle East respiratory syndrome, and Ebola virus disease infection.” “Influenza – H1N1 2009 virus was the first pandemic influenza to develop during the 21st century [2].” The pandemic-related diseases are correlated with major detrimental effects on the environment, ecosystems, atmosphere, and health of national and global communities. We, too, wound up in massive political and social chaos.

2. Introduction

The novel coronavirus spread so quickly that it changed the globe’s rhythm in 2020, as it is an outbreak of full modern global disaster health. ‘CO’ means corona, ‘VI’ means a virus, and ‘D’ means illness. This illness was previously referred to as ‘2019 novel coronavirus’ or ‘2019-nCoV.” “(CoV) is a broad family of viruses that cause diseases ranging from the common cold to more serious diseases such as Middle East Respiratory Syndrome (MERS-CoV).” In December 2019, the “HealthCommission of Hubei Province,” China, first announced the outbreak in Wuhan, China, on 31 December 2019, a cluster of unidentified cases of suspected etiological pneumonia (suspected cases), which is extreme, was first detected in Wuhan City, Hubei Province, China [3]. Despite this, an exceptionally high number of patients in mainland China became diagnosed with SARS-CoV-2, prompting the

Chinese governments to implement stringent surveillance measures. After mid-December 2019, the epidemic of COVID-19 has gone through three stages: Local dissemination, dissemination to the population, and transmission. (i) Local outbreak: The advent of COVID-19 correlated with the world's biggest annual human movement, i.e., the Spring Festival travel season, culminating in a massive domestic and global dissemination of the virus. The (ii) Phase of transmitting to the public:In several groups such as family in Wuhan, inter-personal and grouped transmission happens. (iii) The period of large-scale transmission of the pandemic spread: Most reports were scattered at the early stage of the epidemic, and others were connected to the Huanan Seafood Wholesale Industry. Chinese Government has taken drastic action to reduce the epidemic. Wuhan's municipal Government halted all public transit throughout the region on 23 January 2020 and removed both inbound and outbound travel. The disease speedily increased, spreading from Hubei to other parts of China, while COVID-19 cases gradually increased in other countries [4].

The viruses spread rapidly across the world, and there were many widely scattered clusters worldwide. "As of 14 July 2020, more than 13 million COVID-19 reports have been reported in more than 188 countries and territories, resulting in more than 572,000 deaths; more than 7.22 million citizens have recovered. Cases refer to the sum of individuals tested for COVID-19 who were identified as positive according to approved official protocols.

On 28 January, Dr. Tedros Ghebreyesus, WHO's Director-General, meets with President Xi to discuss the outbreak, emphasizing it as a top priority institution. And then on 30 January, "WHO declares COVID-19 as a Public Health Emergency of Global Concern – this follows 82 confirmed cases outside China,""and as a pandemic on 11 March, [5]" and now there is ("SARS CoV 2") on all continents other than Antarctica.On 5 March, Director-General Tedros Adhamon Ghebreyesus reported that although the disease might be uncontrolled in certain settings, it is not yet uncontrollable, and this will be the criterion to qualify into the concept of a pandemic. "The possibility of a pandemic is becoming possible, and if anyonewants to name the epidemic a pandemic, it will be the first pandemic that could be effectively regulated." Preventive steps to minimize the risk of infection include remaining at home, maintaining distance from others (especially those with symptoms), and washing hands regularly and for at least 20 seconds with soap and water, practice good air hygiene, and do not rub with unwashed hands the eyes, nose or mouth. Given these steps, the pandemic SERS-CoV-2 emerged in the months that COVID-19 transmissions proceeded for the first time after quarantine measures were taken on 18 March 2020. There are no COVID-19 vaccinations and no clear antiviral drugs [6]. The introduction of these steps culminated in closing several businesses, hospitals, and research institutes and limits on travel and social gatherings. People nowadays tend to operate wherever and at any time while staying linked and communicating regularly with friends, like at the main place of work of their employer, or online forums and workshops are common activities for certain individuals. "As of 2 April 2020, the cumulative amount of verified cases exceeded one million [7]."

The new estimates of a simple number of COVID-19 reproductions (R0) in January ranged from 1.4 to 2.5. However, a further study showed it was about 5.7 with a 95% confidence interval ranging from 3.8 to 8.9. The average number can differ across communities and should not be associated with a large number of widely recognized reproductions, named R, provided variables, such as social distancing and social immunity. By mid-May 2020, the effective R was similar to or less than 1.0 in several countries across the world, indicating that the risk of infection in certain areas at the time was constant or reducing[8].It has been used to justify and clarify why lockdowns, social distancing and other preventive measures are required in this pandemic to maintain the count of cases and death tolls small." The higher the R0, the faster the epidemic begins, said and specialist in infectious diseases at Dalla Lana School of Public Health, University of Toronto developed a COVID-19 model for estimating reproduction rates."

2.1. Objective

This research aims at examining the SIR model to simulate the outbreak of a virus over time. The MATLAB programming allows simulation and study of SIR disease dispersion Disease model of parameters varying. It provides a comprehensive system for monitoring and predicting the outbreak in a very simple, effective, and rapid manner. The proposed solution is applied with the models SIR, developed under the framework MATLAB\Simulink. We include some

precise information regarding the present pandemic scenario at COVID-19 and a description of the major computer modeling techniques [9].

3. Literature Review

Mathematical simulation is a broad concept involving a wide number of techniques. Simulation is one form of working it out. "Infectious disease modeling is a method used to research the processes by which pathogens propagate, forecast the potential path of an outbreak, and test methods for managing an epidemic." Mathematical simulations may predict how infectious diseases advance to explain the possible result of an outbreak and better guide public health initiatives. Applications use basic observations or data obtained coupled with estimates to define criteria for multiple infectious diseases [10]. Modeling may help determine which measures to avoid and which potential growth patterns to review, predict, etc., John Graunt was the first physician who explicitly sought to measure death causes in his 1662 book on the Bills of Mortality, Human and Political Observations. Bernoulli was trained as a surgeon and developed a mathematical model to explain the smallpox inoculation process.

Throughout the early 20th century, the rule of collective action was introduced by William Hamer (epidemic). Ronald Ross describes disease actions. Throughout the early 20th century, the rule of collective action was introduced by William Hamer. Ronald Ross explains the epidemic actions.

Compartmental versions appeared in the 1920s. The epidemic model Kermack – McKendrick (1927) and the Reed Frost (1928) model also characterize the connection between prone, contagious, and recovered[11].

3.1. Types of Epidemic Model:

"Stochastic" involves becoming a random variable or getting one, which is a method for calculating probability distributions of possible results by taking into account statistical variability over time in one or more inputs, which depends on the increasing possibilities of cancer and other disease mechanisms.

Mathematical formulas "Deterministic or compartmental" are often used when dealing with large populations. This model classifies individuals within the community into different subgroups or compartments, reflecting a particular disease level. Simulation has immense potential to help manage the global COVID-19 crisis in 2020 and to future pandemics. Open-source programming codes are increasingly important to simulate the virus' complex propagation over a time domain [12].

Any modeling method follows that represents and analyzes the outbreak and combines dynamic variables that can contribute to the outbreak. At the same time, there are several posts on the epidemic outlook for COVID-19. We gathered some of the COVID-19 disease predictions from other researchers, as shown.

3.2. Sir, Seird, Sird Model

The SIR model is a simple model commonly used to describe the transmission of infectious diseases and is the basis of three levels for other models like SEIR and SIRD.

The SEIR model suggests that individuals bear lifetime immunity to disease after healing. However, the tolerance wanes with time with other diseases following infection. The SEIRS model is used to enable the recovered individuals to return to a vulnerable state [13].

With the SIRD model, an extra community is placed into the "Removed" compartment. By the conclusion of SIR, to differentiate between cases rescued and cases of death. The best-established approach for knowing the epidemiology is the standard SEIR approach ("Susceptible-Exposed-Infectious-Recovered"), which is often used at the community level to identify the number of people infected as infectious or show no symptoms to which each person is immune or dies. Individuals classified as susceptible based on the number of effective reproductions with a certain probability of infection. When the R0 is over 1, virus growth will spread further, and the disease will begin to rise. If it goes below 1, the epidemic can occur at a reduced mortality risk because less than one affected patient accompanies mortality or rehabilitation resolution in an earlier event. The R0 has been recorded with very different magnitudes due to changes in the region, culture, measurement, and level of outbreak. Even though it is significant, arriving at an accurate, measured value seems difficult due to data limitations and inaccuracies in reporting. However, it appears difficult to detect R0 explicitly. Some latest research tackles this pandemic through the creation of simulation codes.

If the basic reproduction amount is larger, the overall proportion of contaminated persons in a com-

munity ('attack rate') would be greater. Once R0 is over 3, more than 90% may become contaminated if successful treatments do not reduce the chain of infection transmission [14]. Early in the initial stages of an outbreak, knowledge of the specific replication number is significant and allows politicians to determine how robust the steps required to contain the disease will be.

Strict lockdown measures for fighting the country's 2nd COVID-19 pandemic have been reintroduced in Beijing. When the enormity of the risk became clear, politicians tended to rely on statistical modeling know-how to minimize their effects best, with special measures to focus on whether the curve may be flattened to reduce the healthcare burden [15]. A critical question affecting humanity is how to monitor the infectious disease outbreak and prevent the transmission. Along with the classical LBP, features from the completed modeling of LBP are also utilized for the classification using K-Nearest Neighbor (KNN) [16][17]. The extracted colour based features and LBP features are analyzed independently for glaucoma diagnosis using SVM classifier [18]. SVM classifier calculates a hyperplane that separates the feature space with maximum margin [19]. The complex texture features are discussed in for fundus image classification [20][21].

3.3. Covidsim

This is a COVID-19 epidemiologic model established by Imperial College. "The proposal expected up to 500,000 deaths in the UK and 2.2 million deaths in the US." If, as defined in the 20-page Ferguson Report to British Prime Minister Boris Johnson, the respective governments failed to react, "a central force pressuring the British Government to shift the pandemic agenda" by imposing a nationwide freeze. Perception problems have been posed, as the Imperial College report is a one-sided analysis.

Figure 1 represents the flattening of the curve. It is looking at the benefits of a lockout, without thinking into the prices, which often involves the opinion that any single death is equivalent to every other death. A simulation run using those parameters will give the same forecast always. Somebody in the community I, for example, can infect an individual with S when they interact. Over multiple patterns run, it gives a variety of potential possibilities.

Modelers also replicate various types of human movements. Within 'equation-based systems, people are grouped into community classes However, when groups are split into smaller, more diverse societal sub-sets depict better reality, and then the systems become more complicated. An alternate approach is utilizing an "agent-based method," where each individual moves and responds accordingly.

"We stress that a rigorous research and quarantining scheme is the only possible long-term option before a vaccine is discovered" (Menon). "Instead of just stressing that such mechanisms do not quantify the

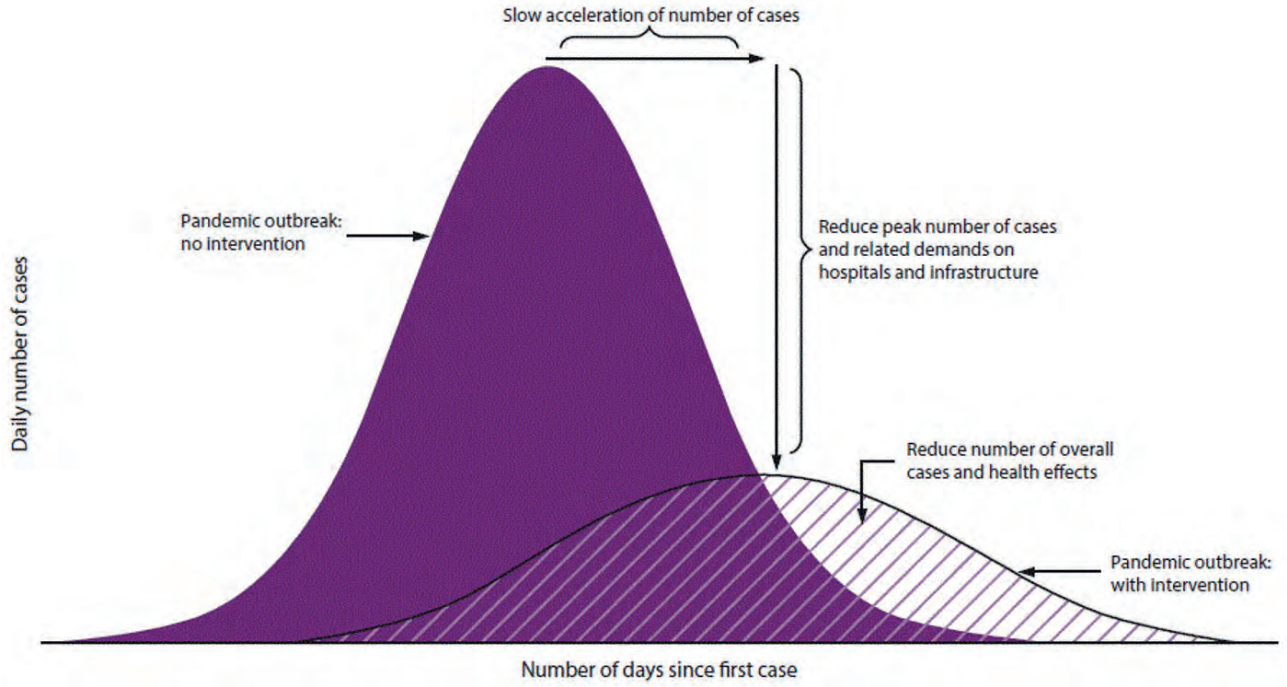

Figure 1
Flattening the curve(Image: ©)CDC

economic lockdown costs, transport opening Pan-India is not a good idea as per our model" (Pujari). In addition to this, quarantines are successful in reducing the number of citizens vulnerable to disease, and even more complex attempts to combat the far larger real-world COVID-19 outbreak. Policymakers utilize these and many other measures to prevent the spread of the infection. Their success can influence if the outbreak is wiped out or continues to grow. Studies conducted by Imperial College under the guidance of Neil Ferguson showed that "before vaccination is practicable (inevitably 18 months or longer), social distancing and other steps would be needed"

3.4. "Flattening the Coronavirus Curve: What This Means and Why It Matters"

As currently, there is no available coronavirus vaccine and testing in many nations is relatively limited. "The WHO has emphasized the need for people to take constructive measures to reduce the spread and flatten the curve said WHO Director-General Tedros Adhanom Ghebreyesus" at Wednesday's media briefing.

The curve shows the number of new cases expected over sometime for epidemiology. Despite a drastic rise in coronavirus infections, the same amount of patients infected at each stage will see a steadier spike in cases without overburdening the healthcare system.

"Flattening the curve refers to measures of community isolation, which maintain the daily number of cases of disease at a manageable level for medical providers"

The most significant suggestion is to slash transmitting speeds by observing good grooming practices and exercising mutual distancing. Public health experts claim the increase may be stopped, whether individuals practice "internal distancing" by avoiding public places and restricting their travel in general. Now, COVID-19 will tend to grow rapidly for months without any efforts to slow it down.

3.5. Analysis

3.5.1. *Coronavirus: What Is, And Will It Work, 'Flattening The Curve?'*

Working with specific reasons impacting the disease's propagation, we can understand how we can work our way to curtail this COVID-19 outbreak and flatten the curve. The SIR model is included in the present analysis. It simulates the SIR process for the transmission of infectious diseases. The simplistic model developed in 1927 is composed of three models: susceptible (S), infected (I) recovered (R).

1. Susceptible: Individuals who never had the disease and who can catch it.

2. Infected: Those that are currently infected from the disorder and are infectious.

3. Recovered: People who have developed the illness previously and who are resistant. Any individual belongs to one of those groups.

As there is no antidote created for this disease yet, we may assume the whole society is vulnerable to this disease to become affected. Therefore the whole population will constitute the "susceptible" container because there is no vaccination yet created for this disease. We may assume the whole society is vulnerable to this disease to become affected. Therefore, the whole population will reflect the "susceptible" area.

An individual at the "susceptible" stage will move to the next (infectious) stage of the model by contacting an infectious human. This single move decreases the number of susceptible people by one, respectively.

The next area is for those contagious individuals who carry the illness who are likely to transmit it to other individuals. Once recovered from the illness, infected persons will switch to the "Removed" room.

The container excluded contains those no longer infected, including others who suffered from the illness (closed cases).

In the SIR model, the estimation of these three compartments stays unchanged and matches the initial population. Those are the parameters we want to model & approximate, such that the cases recorded and simulated are approximately identical.

The initial number S (0) is the general group impacted by the outbreak, while I(0) is the total of reported cases that may be any amount but not zero. If the starting times for spread and simulation are similar, we can set R (0) to zero. The transmission rate decreases in a monotonous way over time.

Mathematically, the following differential equations can be used to describe a typical SIR model: DS dt = − β N SI (1) dt = β N SI − πI (2) dRdt = ÿI (3), where N corresponds to total population number, N = S + I+ R and the normal birth and death rates are overlooked.

Therefore, the sum (N) = (S) = (I) = (R).

The SIR model provided us a significant prediction metric called the "basic reproductive number,"

or R0 that ratio calculates how infectious an illness is, that is, how many individuals can a single sick person contaminate. If R0 > 1, the epidemic spreads, which is an important indicator of a pandemic? If R0 < 1, the spread is down

% Np = the population of the community. (Default = 100, so you easily read the percentage of the community infectious/infected)

% Ni = the number of index case (initial infectious individual, Default = 1).

% Ds = is the minimum safe distance below which the probability of being

% infected is Prinf (Measure of how contagious the disease is:

% Lower means more contagious. Default = 0.05).

% Prinf = probability that you will be infected if you are closer than Ds

% to an infectious individual (Measure of how precautious people are washing hands, not touching mucus membrane Default = 0.2)

% Tr = Time it takes for an individual to be removed from the population

% (Death, Quarantined, Recovered and become immunized. Default = 1).

% F = Relative repulsive force strength (measure of social distancing Default = 1)

% video name = Simulation video file name

You can see how the Ds (a measure of contagiousness of the disease), Print (a measure of how practices personal hygiene), Tr (a measure how quickly people recover, die, or get quarantined by the Government) and F (a measure of how people adhere to social distancing) affects the rate of spread and helps flattens the curve or aggravates the situation.

3.6. Factors Considered Here:

1. All people randomly move
2. 50% of population stays home
3. 90% of population stays home

So, the default population sample size is 100, which we are trying to study the spread of the disease that has been affected.So, let us look at different cases and then see how the change of any of these parameters affects the disease's spread.

- Population size = 100
- Minimum safe distance = 0.05
- The probability of getting affected if you are within that distance = 0.02
- The measure of social distance =1

Figure 2 simulation graphs show that infected individuals with color range red are infected, and the susceptible people are green. Those who are removed from the model are blue. As you can see in this picture, 50% of the population is infected at the pandemic's peak when they are talking about flattening the curve.

3.6.1. *All People Randomly Move*

From Figure 3, you can see that by day 22, the disease quickly spreads from one person to the entire population. Note how the red curve line reflects the number of people affected, increases as the disease, SPREADS, and then tappers as people recover.

3.6.2. *50% of Population Stays Home*

If we are talking about social distancing, taking precautions, the impact is very dramatic in how contagious the disease. You see from Figure 4 that 50% quarantine does not work because all people got a virus. A good result is a 20% reduction in peak.

Hopefully, there are lots of options to avoid an outbreak. In all, health authorities urged individuals to

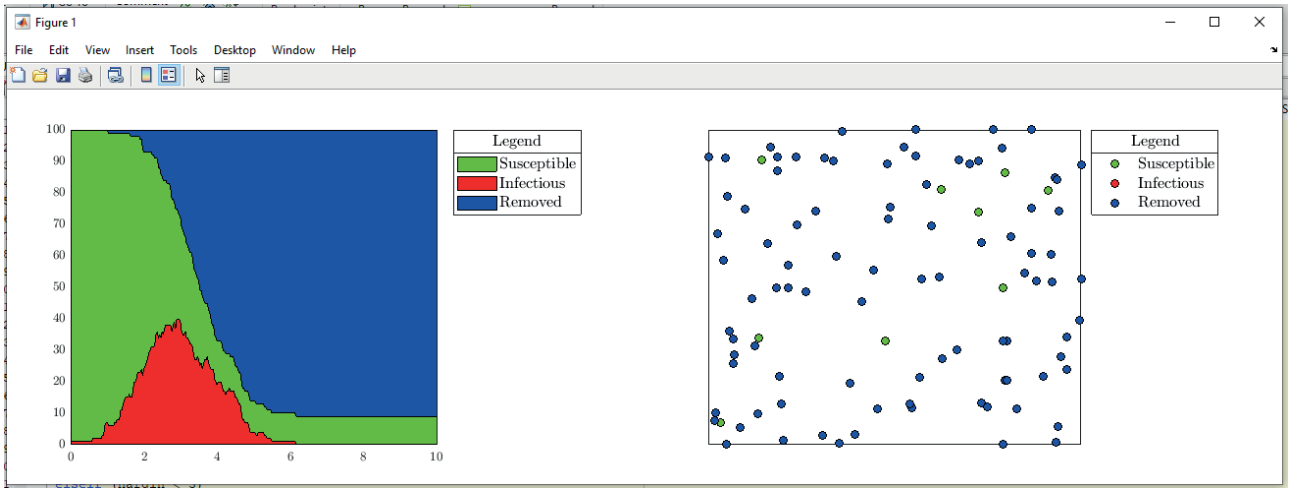

Figure 2. Simulation Graph

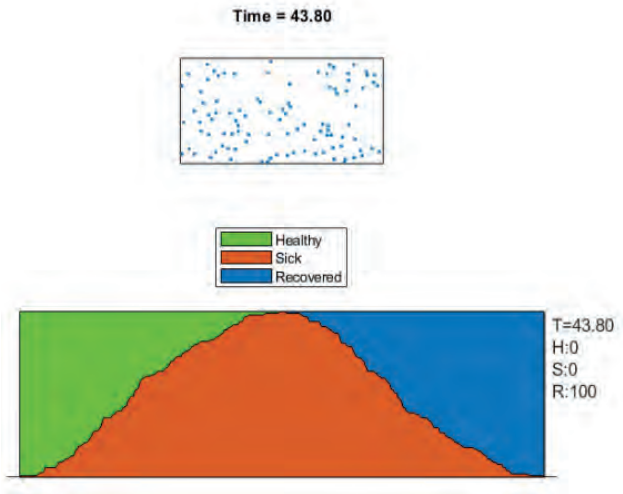

Figure 3. All People Randomly Move

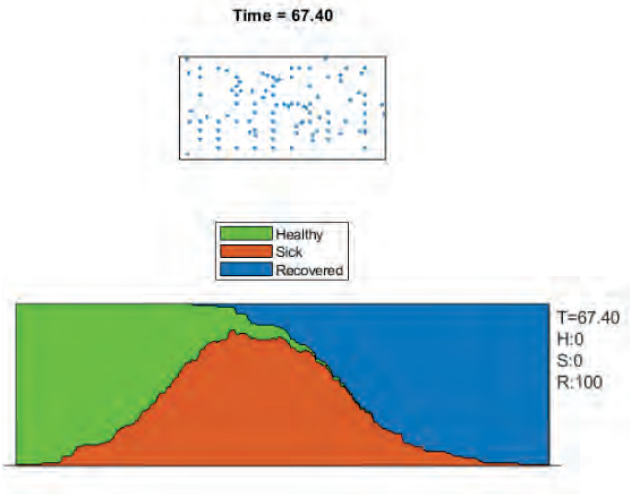

Figure 4. Population Stays Home

skip public gatherings, remain home more frequently and maintain their distance from others. As individuals are less aggressive and interact less, the risks of transmitting the infection become fewer.

- The minimum safe distance

DS 0.04 = 20% reduction in the measure of contagious By reducing it to 20%, it doubles the number of the individual in the community that was not affected and then reduced the percentage of the maximum number of infections at any particular time to 20% from around 50%, so this helps to flatten the curve.

- ES=0.05

A few people are still heading out. Because of their job or other responsibilities, they might not be willing to remain home, or maybe they just fail to obey public safety alerts. Such people are not only more likely to get infected themselves, but they are also more likely to spread illness. Individuals do not take adequate care, lock heads, do not wash their faces, so they hit the 50% risk of being infected.

- Print F = 0.05

Here, we see that by increasing the probability of infection, the maximum number of cases go away by about 70%, and only one individual remains unaffected throughout all the time, and everybody got infected

- Probability 0.02

Government responsiveness, lockdown or the case where the disease is deadly that you can get affected, **and then instead you have been removed or die in half of the day** = 0.05 **or** Government is very responsive in that if you get the infection immediately with the strict measure you recovered from the population.

- CR= 0.5

Nobody got infected. The single person in the population did not die or be removed or quarantined, or covered. People are not practicing hygiene; the people get infected or die, **recover because** people are careless

- Social distancing: F = 4 /5 More social distancing makes people safe, and by reducing their **allure**, individuals may be nudged off public spaces

3.6.3. *90% of Population Stays Home*

Let us see what happens as we decide to shift about a fifth of our population when the remaining three quarters follow a practice of what health professionals' term "social distancing."

From Figure 5, when people stay at home, in this case, the virus infects only 54% of the population, and at the peak of the disease, we have only 35-40% of sick people.

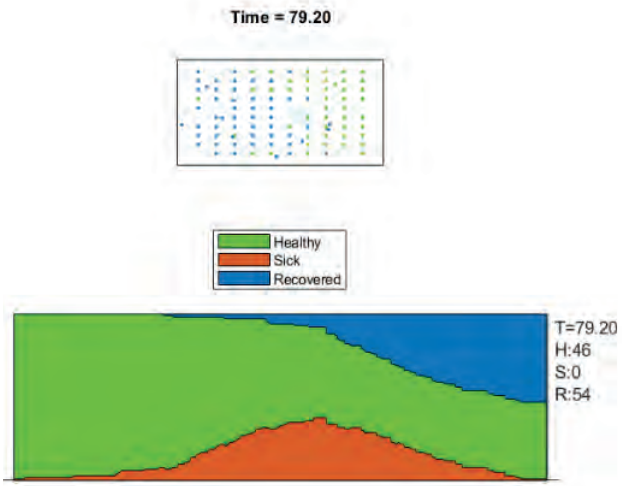

Figure 5. When People Stay Home

4. Methodology

We explained a mathematical model, which explains COVID-19's transmission dynamics determined using MATLAB's parameter estimation methodas follows: susceptible, exposed but not yet infectious, infectious and removed, i.e., isolated, recovered, or otherwise no longer infectious and their compartments coded under the MATLAB\Simulink. Information resources on coronavirus outbreak and pandemic history, Countries implement online journals, downloaded databases, news articles, and various simulation models on coronavirus outbreaks. Software and methods used, such as MATLAB, provide a mathematical model prediction.

5. Results and Discussion

More than 2.5 million individuals became affected by the COVID-19 pandemic and have increasingly become a significant danger to health worldwide. Modeling and simulation methodologies are multiple. This paper provides a systematic method to tracking and predicting virus propagation worldwide in a simple, secure, and quick way through various open-source programs. Transmission of infectious disease is a dynamic mechanism of transmission that happens inside the public to forecast the potential pattern of infectious diseases accurately. Therefore to control or reduce the harm of infectious diseases, it has become important to research the testing and production of predictive models for infectious diseases.

6. Conclusion

Using the easiest example, you are forced that strict quarantine will significantly minimize the number of ill people and the spread of the disease. However, with varying outcomes, modest social differences typically outperform the quarantine effort, and severe social distancing generally performs well, which summarizes the results. Severe social distancing generally performs well. Figure 6 is the summary of the results.

All citizens randomly moved beyond three scenarios. An attempted quarantine, including 50% of the population stays at home, and 90% of the population stays home by exercising modest social distance, or extreme social distance is random,which implies the growth has seen unusual outcomes. The curve takes on multiple forms, depending on the degree of virus propagation, which will be a steep curve. The infection grows steadily (i.e., case numbers tend to multiply at a constant rate). The cumulative number of cases would rise to its height within several weeks. There is also a significant decline in infection rates after a sharp rise; the number of cases often decreases steadily when anyone who may get infected is diagnosed with the infection. The sooner the infection incidence rises, the quicker the local health care network's burden shifts beyond its capacity to cope with patients.

Future Scope

We will investigate how contact tracing with a restrictive but not completely locked down regime can be used together in future work, which is a basic model, which is useful for informing and recognizing the effects of initiatives, but quantitative models are far more complicated.

The time points in which the data continuously moves are immediately excluded from the results. Absolute or partial lockdown, social distancing, quarantine, isolations containment interventions can impact the virus's propagation and flatten the curve quicker if these steps are enforced earlier. These interventions affect the chance of infection, which results in a decrease in the beta function.

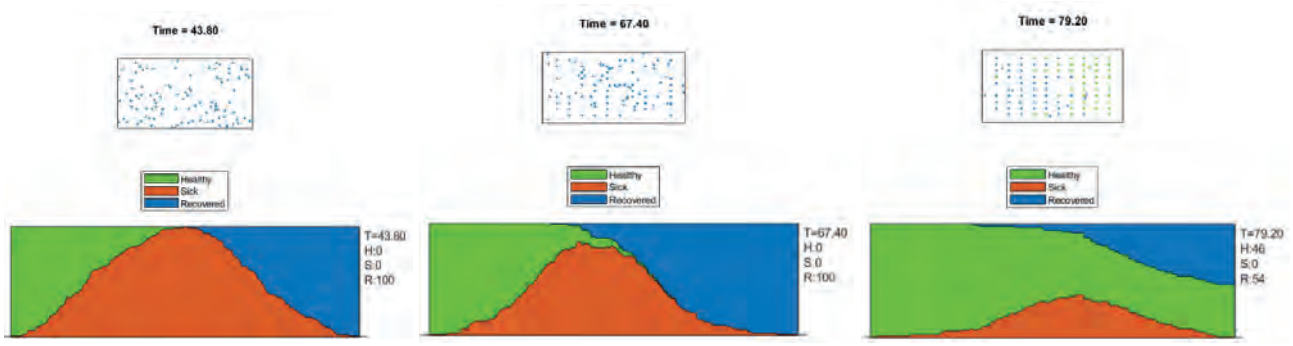

Figure 6. Summary of Results

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Healthcare consumer behaviour: the impact of digital transformation of healthcare on consumer

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Abstract

Healthcare consumer behavior is influenced by the cumulative impact of internal/external factors. Individual considerations, and interplay amongst determinants, are both crucial. Today, customers demand more information, greater options, and real-time interactions. Customer engagement has become crucial. Digital Transformation with emerging technologies like AI, Blockchain, Telemedicine, etc., helps physicians, optimizes systems, improves patient experience, and reduces human errors.

This paper discusses factors influencing healthcare consumers' behavior and provides insights into digital technologies to enhance the consumer experience. The qualitative method is used by engaging a closed consumer group in discussion and through in-depth interviews. The analysis provides an insight into the behavior of healthcare consumers.

The study finds that the new breed of consumers is well informed about healthcare providers' digital readiness. The factors influencing consumers to select healthcare providers include digital readiness of the healthcare provider, good customer experience, word of mouth, and brand image.

Keywords

Digital Transformation, Healthcare services, Consumer behavior, Impact

Imprint

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1. Introduction

The healthcare industry is currently experiencing a new wave of opportunities. The pattern of consumer purchasing is changing due to the influence of various internal and external factors. The internal aspects may be personal and psychological, and the external ones mainly consist of cultural and social issues. A deep knowledge of consumer behavior in health services and factors influencing it is required to design healthcare marketing strategies. Healthcare services consumers' attitude has different perspectives. It depends on the needs and consumption motivations, but it depends on the complexity of the services.

Consumer behavior in the healthcare sector results from various motivators - stakeholders including doctors, opinion leaders, and family members, who greatly influence an individual. Health services consumers, particularly, differ from other types of consumers because of certain specific requirements, arising from the market's particular characteristics, supplier-consumer relations, and how a particular healthcare system is organized, are different from other fields' consumers and are limited. In the healthcare sector, anybody can become a consumer at any moment, which indicates a huge potential market. [1]

1.1. Categories of Consumers in the Healthcare Sector

The consumers in the healthcare sector can be categorized mainly into four groups. The first category includes people facing severe healthcare problems and requiring highly specialized health workers and sophisticated machinery; the second consists of people who voluntarily visit healthcare centers for routine investigations, and the third category includes people who opt for certain services but do not pay regular visits to the health centers. The fourth category consists of people who treat themselves independently and often do not rely on medical services. They often rely on internet facilities and drugstores for self-medication. They might go for 'over the counter drugs or opt for alternative medicines and treatments.

1.2. Enhanced Consumer Experience through Digital Transformation

Through digital transformation, consumer engagement and experience in the healthcare industry have

improved. It is quite evident that for many years healthcare sector has operated on an experiential level where consumers mainly relied on the expertise of doctors or other healthcare service providers. Customer engagement was when needed, with a minimum level of transparency within the ecosystem. Hence, digital engagement was not required. Today, the scenario is evolving. Consumers in the sector constantly compare their digital experiences and have expectations of quality service. [2]

The entry of non-traditional healthcare providers has completely changed this scenario. Another important factor accelerating this change is the introduction of disruptive technologies in the healthcare sector. These include wearable monitoring and reporting devices, remote nursing and care, VR (virtual reality) and AR (augmented reality for medical diagnostics and treatment, and Artificial Intelligence application for treatment and personalized prescriptions. Technology companies like Amazon, Apple, and Google, are fast dominating the sector. They are experts in the consumerization of entire sectors, which has created innumerable opportunities in the healthcare sector for customer engagement.

A well-informed consumer base will immensely benefit the health and wellness sector. Better customer engagement and more dynamic decisions making will lead to greater wellbeing.

The discovery and application of disruptive technology drive the development of medical devices. Consumers are experiencing a major change as technology companies obtain approvals for such devices from Food and Drug Administration (FDA). This market segment has witnessed technology transformation that caters to domestic use, for example, portable monitors for electrocardiograms and blood glucose connected to smartphones.

The democratization of consumer health data reinforces the consumer's ownership of large data based upon customer behavior. For example, a scenario where the healthcare provider enables the consumer to share health attributes like heart rate, sleeping patterns, physical activity details, etc., through a wearable device. A new algorithm can be derived that summarizes and highlights problems that will allow the physician to gain insight into their habits and support the consumer in their health journey. All of this will ultimately help to provide a better diagnosis. [3]

1.3. Digitization Improving Healthcare Engagement

The healthcare industry needs to stop thinking of people as patients and engage them as empowered and informed customers. The consumer is supposed to make decisions about their health, though they are undergoing medical treatment. Digital healthcare can make understanding easier and accelerate consumers' engagement and enable healthcare providers to make better diagnoses.

"Artificial intelligence (AI) and machine learning will leverage massive amounts of data to power greater insights, improve diagnosis and treatment, and support consumer health decisions. Digitization of the healthcare experience will simplify the consumer's experience because the data -- whether it is recent test results or heart rate data from a wearable device -- will be immediately accessible versus today's experience of having to answer repetitive questions and get re-tested for things like blood pressure at every visit. The linchpin in this transformation is a new way of thinking about health data. It must be cloud-based, owned by the consumer, and available to share with their healthcare professionals and family members. A centralized, private, and secure cloud-based Electronic Health Record(EHR) will open up the ability for healthcare providers to deliver a simple, contextualized and personal experience that supports consumers in maximizing their whole health." [4]

2. Objective of the Paper

This paper focuses on consumer behavior in the healthcare sector and how the digitization of healthcare services impacts consumers at large. It discusses various factors influencing the behavior of consumers in the healthcare sector. The paper discusses the digital transformation in the healthcare landscape and provides insights into how healthcare services adopt various technologies to enhance the consumer experience.

3. Literature Review

3.1. Factors Influencing Consumer Behaviour in Healthcare:

Various factors impact consumer behavior in the healthcare industry; service quality is one of the most important aspects influencing a consumer. There are five aspects of service quality which include various

tangibles like Physical facilities and equipment, and intangibles such as the appearance of service providers, Reliability (Ability to provide dependable and appropriate service), Responsiveness (Prompt customer assistance), Assurance (Ability and competence of service providers to get patient trust) and Empathy (personal care with an understanding of patient problems), and [5] whether a consumer will revisit the healthcare provider also largely depends on how much the consumer likes or dislikes the service after experiencing it. Also, Word of Mouth (WOM) Communication is important for persuading consumers to visit the same healthcare provider again. In some cases, WOM has been identified as one of the major influential factors in consumer repurchase decisions and a vehicle to express satisfaction or dissatisfaction with a service experience. Another construct that plays an important role is the 'repurchase intention,' which is considered a personal aim to sustain a relationship with the same service provider (in this case, it will be the healthcare employee). In this case, also, WOM is a driving factor. Healthcare providers need to provide service that is sufficient and dependable.

Proper care in healthcare has become an important factor for patient satisfaction. Health care services have to be a client (patient) oriented. The key factors that affect patient satisfaction relate to admission diagnostics, service provider behavior, hygiene, quality of nurses, nourishment provided, dialogue, physician interaction, attitude-behavior, and accessibility of maintenance and housekeeping staff. Healthcare service providers must aim at the best possible services for all patients.

3.2. Impact of Healthcare 2.0 on Consumers

Healthcare 2.0 is a network of applications and services delivered through the Web, which provides up-to-date information and services based on data generated from commercial and individual sources. It also empowers the consumer and helps create a user-rich experience. Personal Health Records (PHRs) enable patients to track their health-related information and take control of their health. The Internet has provided consumers with easy access to health information.

The new breed of consumers who have greater access to information about the healthcare systems has redefined the patient-physician relationship. Seamless exchange of medical information of patient's health through various mediums like healthcare portals, web pages of the healthcare provider, and e-mails helps in better health communication. Consumers are more engaged and seek more information related to their health as well as healthcare systems. Healthcare 2.0 provides a platform that helps consumers stay connected through blogs and other web-connected platforms and addresses several medical conditions outside the physician's office. Decision-making related to healthcare is affected majorly due to more awareness on the consumer's part. [6]

Telehealth and Web 1.0 aims to reduce the gap between the patient and healthcare provider. The online medical record helps in compliance with standard protocols for treatment. Telehealth systems help in reducing costs in home health agencies. Healthcare providers also provide portals to schedule appointments with physicians, demand renewals for prescriptions, access lab test results, and access their health records online.

3.3. Digital Transformation in Healthcare Sector

The healthcare sector is rapidly moving towards digitization and data analytics on a large scale. Data provides a scientific approach to healthcare. Diagnostics are insufficient without scanning and imaging; treatments depend on data analysis of clinical and epidemiological research. Management of data and its volume is no more challenging. The healthcare model is increasingly shifting towards patient-centric designs, which has encouraged healthcare digitization, leading to mobile health (mHealth). It comprises mobile apps, mobile-connected wearable and wireless gadgets, hand-held scanners, and technologies using miniaturized sensors.

The healthcare industry has come a long way from paper-based methods to cloud-based servers to accommodate medical records in a secured manner with some integration level to other systems. We are looking at more precision in medicines and better health care, more accurate and speedier diagnosis. More and more healthcare organizations are adopting blockchain to provide transparency and security of medical data. It helps to improve patient's data privacy and store their medical records securely in digital format. [7]

Digital transformation in the healthcare industry has accelerated innovation in healthcare services. Technologies like Augmented Reality (AR) have much potential to transform healthcare processes and

healthcare management. AR smart glasses such as Microsoft HoloLens, help in augmenting the user's field of view with virtual information, it can be operated hands-free and will not interfere during the work of the doctors while providing access to an information system.

4. Research Methodology

The Research Methodology adopted to achieve the objective of the research paper is qualitative research. The methods used are closed group discussion and in-depth interviews. The closed group discussion was held among consumers of different age groups. The in-depth interview was held in two parts. In one part, consumers of different age groups were interviewed, and their opinions were recorded. In the second part, people working in the healthcare sector (including doctors) were interviewed, and their opinions were recorded. [8]

4.1. Research Questions

Part 1 (Closed Group Discussion)

1. Personal Information Details such as Name, E-mail Id, Gender and Age Group
2. How often do you visit a healthcare center?
3. How often do you refer to online sources for medication?
4. What are your criteria for selecting your healthcare provider?
5. Are you satisfied with your current healthcare provider?
6. As a consumer, what is/are the factor/s for choosing your healthcare provider?
7. Do you prefer to revisit the same healthcare provider?
8. Is your healthcare provider digitally well equipped?
9. Are you aware of the technologies used by your healthcare provider to enhance customer experience?
10. If yes, can you mention the technology used by your healthcare provider?

4.1.1. Research Analysis (Part 1)

A group of forty consumers was identified and engaged in a closed group discussion. The age group of the consumers is between 24 and 50 years. Their opinions were recorded and have been presented in a graphical format for better understanding. The consumers were divided into five groups, and their opinions towards each of the questions were noted to understand their perspective. The main objective to carry out this group discussion is to understand consumers' category, awareness towards technologies, and the impact of digitizing healthcare on them. Points of discussion from each of the groups were compiled. An online questionnaire was floated just before the discussion to collect data. [9]

Question 1- Personal Details

- **Gender Division**

The Gender ratio among the sample size has been represented in a pie chart shown in Figure 1 below.

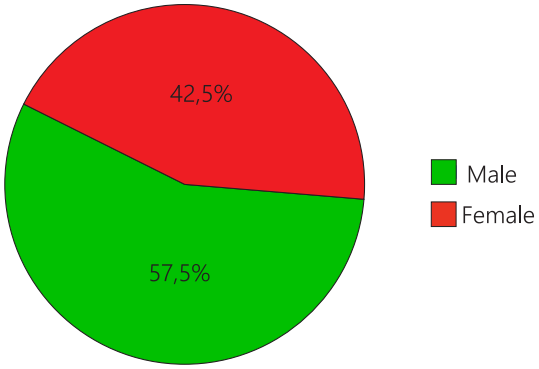

Figure 1: Gender Division

- **Age Group**

The age group considered for the study is 18-27 years, 28-37 years, 38-47 years, 48-57 years, and 58 years and above. Figure 2 shows the Age Group.

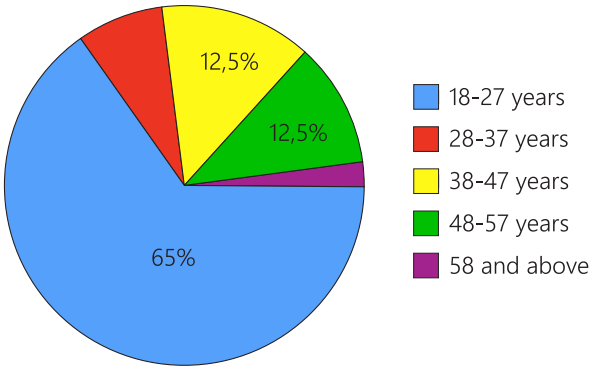

Figure 2: Age Group

Question 2

This question helped analyze the frequency of visits made by the consumers, which gave an idea about users' categories. As shown in Figure 3, the consumers (30%) visited the healthcare center once a quarter. [11]

Summary of Discussion:

- Most of the consumers visited the healthcare center once a month.

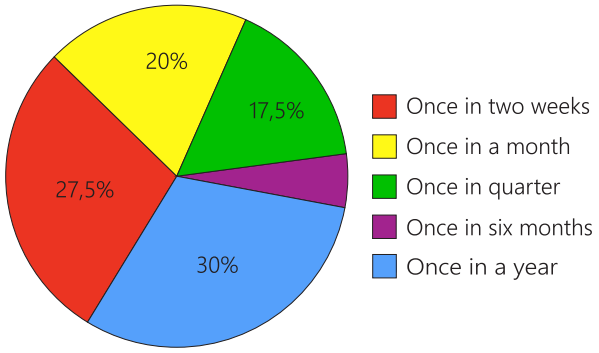

Figure 3. Frequency of Visit to Healthcare Centre

- The consumers mainly belonged to the second category of healthcare consumers, including people who voluntarily visit healthcare centers for routine investigations, which mainly comprised of the age group which was 18-27 years and 27-37 years.
- The consumer group aged 38 years and above was frequent visitors to the healthcare center due to some major healthcare problems.

Question 3

This question also helped to analyze the consumer category, which also helped to understand whether the consumers considered online sources to be reliable for medication. It can be seen from Figure 4 that 37.5% of the consumers refer to online sources for medication sometimes. [10]

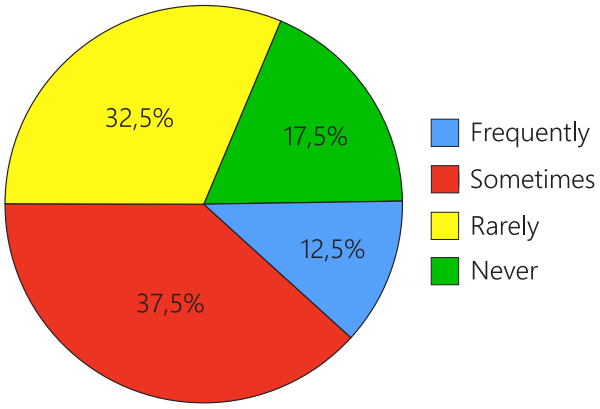

Figure 4: Reference to Online Sources for Medication

Summary of Discussion:

- Consumers aged between 18-27 years sometimes refer to online sources for medication. Most of them refer to online sources to check about the composition of medicines, alternatives to the medicines prescribed by their doctors, and the side effects of medicines.
- Consumers aged above 38 years do not find online sources reliable to refer for their medication. They prefer going to the pharmacy or to a doctor to get advice on medicines.

Question 4

This question helped to understand the criteria for selecting healthcare providers, giving a clear understanding of whether the consumers prefer reputed hospitals, local clinics, family doctors, or any other healthcare provider. As depicted in Figure 5, the majority of the consumers (60%) prefer to go to reputed hospitals like Fortis, Apollo, etc. [12]

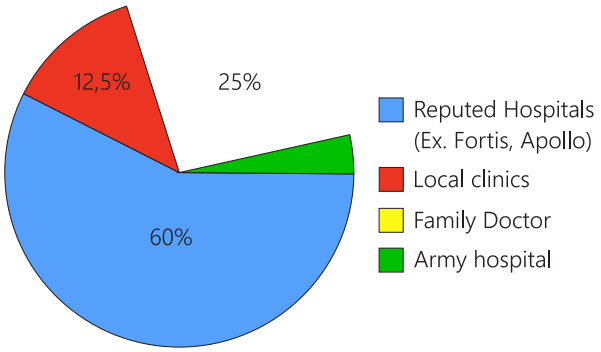

Figure 5: Criteria for Selecting Healthcare Provider

Summary of Discussion:

- Consumers between 18-27 years, 28-37 years, and 38-47 years mainly preferred going to reputed hospitals. They believed that they could trust the healthcare services provided by these hospitals.
- Some of the consumers (approximately 25%) aged between 18-27 years and 28-37 years preferred going to family doctors, especially during an emergency, as they believed they provide better care and medication. Trust factor also plays a major role in this case.
- Consumers also had an opinion regarding visiting government hospitals. During the discussion, most of the consumers did not prefer going to Government hospitals due to lack of infrastructure, unavailability of proper nursing staff and doctors, lack of cleanliness, and as these hospitals lagged behind private hospitals in being digitally well equipped. Although one of the consumers (aged 27 years) believed that doctors' quality in Government hospitals is very good, people avoid going to the government hospitals due to these factors. [14]

Question 5

This question helped to understand consumer satisfaction regarding their current healthcare provider. As depicted in Figure 6, most consumers, i.e., 90% are satisfied with their current healthcare provider.

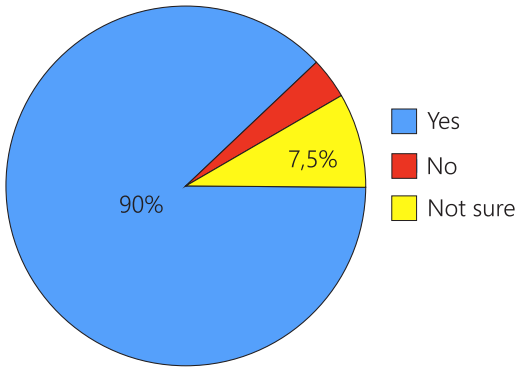

Figure 6. Customer Satisfaction with Current Healthcare Provider

Summary of Discussion:

- Consumers were satisfied with their current healthcare provider regarding service, facilities, and quality of treatment.
- One of the consumers was not satisfied with their current healthcare provider due to long wait hours and lack of care beyond the doctor's office.

Question 6

This question helped to understand the various factors influencing consumers to select their healthcare provider. The factors included healthcare centers being digitally well equipped, customer experience, brand image, online ratings, word of mouth, cost, and other factors like the doctor's experience, effectiveness, and a major role in selecting healthcare providers. As depicted in Figure 7, customer experience can be considered a major influencing factor, followed by the healthcare center being digitally well equipped and then word of mouth.

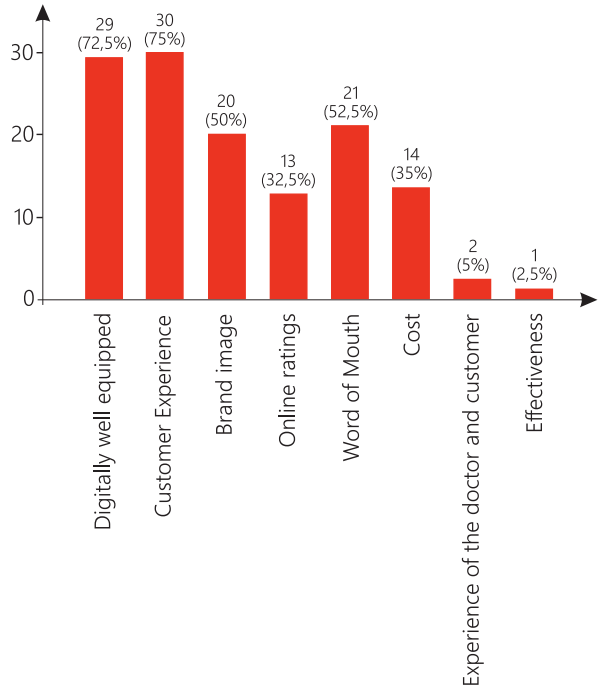

Figure 7. Factors for Selecting Healthcare Provider

Summary of Discussion:

- It was noted that digitization had a huge impact on consumers. They wanted their healthcare providers to adopt the latest technologies to provide them with better diagnoses. The consumers believed that the present healthcare infrastructure needs to be transformed digitally in all quarters and levels. One of the consumers opined that in recent times of COVID-19, with the scarcity of physical hospital appointments, the entire healthcare system should channelize its operations to provide services using digital platforms.
- Word of Mouth, especially from reliable sources (for example, patient's relatives, close family members, friends), played a major role in determining healthcare providers' choice. [15]

Question 7

This question helped to understand customer loyalty towards their healthcare provider. It can be seen that the majority of the consumers preferred going to the same healthcare provider. Figure 8 shows Customer Preference for Healthcare Provider.

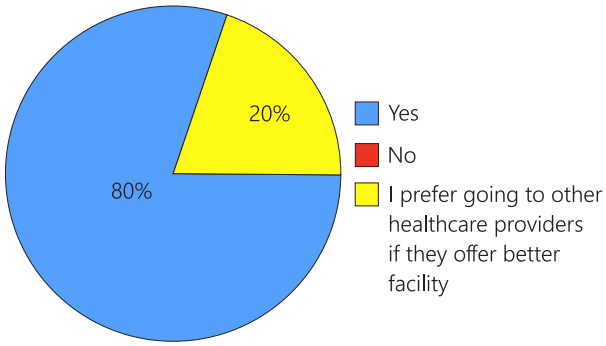

Figure 8. Customer Preference for Healthcare Provider

Summary of Discussion:

- Customers were mostly loyal towards their healthcare providers because of the trust factor.
- 8 out of 40 consumers preferred going to other healthcare providers if they were offered better services, customer experience, better technologies, and better offers.

Question 8

This question helped to understand whether the consumers were aware of whether their healthcare pro-

viders were digitally equipped or not. It was also useful in analyzing whether most of the healthcare providers are digitally well equipped or not. It can be noted from Figure 9 that most of the healthcare providers (67.5%) that the consumers visit are digitally well equipped.

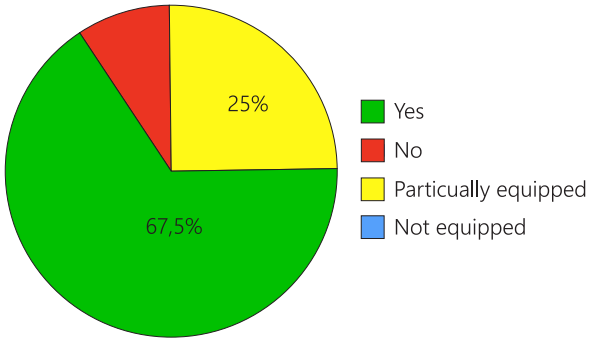

Figure 9. Digital effectiveness of Healthcare Provider

Summary of Discussion:

- The consumers between the age group 18-27 years and 28-37 years were more aware of the technologies used by their healthcare providers.
- It was evident from the discussion that consumers preferred hospitals that were digitally well equipped.
- It was also noted during the discussion that the consumers in the age bracket of 38 years and above were unaware of whether their healthcare providers adopted the latest technologies to enhance their experience.

Question 9

This question helped to give a clear view of whether consumers are aware of the latest technologies adopted by their healthcare providers. As seen in Figure 10, a mixed response was obtained from the consumers.

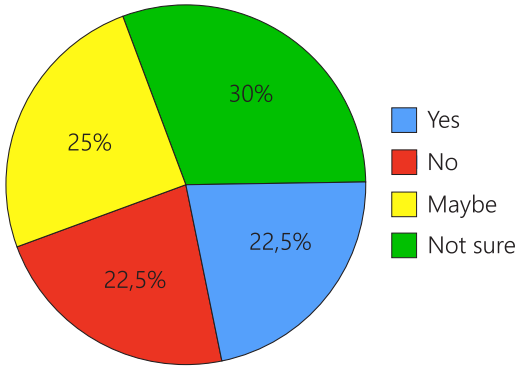

Figure 10. Awareness Regarding Digital Readiness of Healthcare Provider

Summary of Discussion:

- The consumers in the age bracket of 18-27 years and 27-37 years were more aware of whether their healthcare providers were digitally equipped or not.
- There is an equal distribution of unaware people, not sure or did not know about their healthcare centers' digital readiness.

Question 10:

This question helped to understand various technologies that create awareness in consumers, which also helped to understand the technologies adopted by healthcare providers to provide a seamless customer experience to their consumers.

Summary of Discussion:

- Consumers were aware of Electronic Health Record system adopted by their respective healthcare providers to store their records.
- Consumers were also aware of the various Apps used by their healthcare providers to provide those services digitally.
- Some of the consumers were aware of the adoption of Artificial Intelligence by their healthcare providers.

4.2. Research Questions

Part 2(In-depth Interview)

Consumer Perspective:

1) Are you aware of any technologies used by your healthcare provider? (e.g., any specific app, tools to monitor your health, specific technology like AI)
2) If your healthcare center is digitally well equipped, how has it improved your experience?
3) Do you use any wearable and wireless device? (e.g., fit bit, MI band) Does your doctor keep track of that?
4) Would you prefer care beyond the doctor's office? (For example. Request prescription refills electronically, receive reminders {via e-mail or text when it is time for follow up care}, communicate with your provider through secured mail, use remote or telemonitoring devices to monitor and record your health indicators)
5) Any improvement that you would like to suggest to your healthcare provider to improve your experience? (It can be related to technological aspect, service aspect)

Healthcare Provider Perspective:

1) What are the technologies used by your organization to enhance customer experience?

2) Is your organization taking any steps to make consumers aware of the technologies used?
3) What, according to you, are the important factors influencing consumers to opt for a particular healthcare provider?

- *4.2.2. Research Analysis:*

Responses as per Consumer Perspective:

A total of ten consumers were interviewed in-depth. The opinions of the consumers are based on both private hospitals and government hospitals.

(Age group varying between 24 and 50 years)

Question 1:

- It was noted that the consumers of age groups ranging from 24 to 30 years were well aware of the technologies used by their healthcare provider.
- There were also some opinions about government hospitals, which lagged in terms of being digitally equipped.
- Points covered by the consumers are as follows:
  a. Reputed healthcare providers like Apollo use the personal assistant app to provide services like online appointments. The app uses the patient's personal information to provide online consultation, and the data is stored online. The consumers do not have any issue in providing their personal information to such reputed hospitals. Also, consultation is provided by the doctors via video calls in case of an emergency.
  b. Hospitals like Fortis use EHR and EMR (technologies) to store patient's data. EHR is an electronic health record number, consists of all the healthcare records information, and maintains data confidentiality. EMR (Electronic Medical Record) number is used for first-time registration. These technologies are used to store patient's information to provide them.
  c. Private hospitals have adopted various technologies well. BM Birla hospital uses a digital watch connected through an app to monitor patient's movement in the hospital.
  d. QR code-based Apps are provided by certain hospitals and laboratories where patients can get the e-report of their tests by scanning the QR code (which is unique to each of the patients) provided to them by the hospital.

Question 2:

- The consumers felt that digitally well-equipped hospitals provide them with a better experience, whether it's about maintaining their records or better diagnosis.
- Government hospitals are still not equipped digitally.
- Apollo Hospitals provide Health cards, where the patient's data can be updated online without having to visit the hospital frequently.
- Since the hospitals have adopted various technologies (like a laser, for example), the operation time is minimized.
- With the help of Apps, it is easier to book appointments, and also, it is easier to locate hospitals present near one's location.
- E-Prescription facilities have enabled patients to have their records handy.

Question 3:

- Some of the consumers used Fitbit, Mi-bands to monitor their health.
- One of the consumers reported their data (recorded in the wireless device) to their doctor.
- The consumers also came up with opinions about using electronic devices like Accu-Chek and Omron BP Monitoring System. (3 out of 10 consumers aged 35 and above used health monitoring devices to track their health).

Question 4:

- Consumers preferred care beyond the doctor's office. They preferred to have follow-up reminders, e-prescriptions, and blogs to be shared via e-mail.
- Care beyond a doctor's office cannot be available in government hospitals as they do not have such facilities.

Question 5:

- In terms of services, one of the consumers had an issue regarding interns who perform basic services like injecting syringes; he believed the interns had a laid-back attitude, due to which he had to suffer.
- One of the consumers also had an opinion regarding government hospitals having a lackadaisical attitude towards adopting technologies. He believed private hospitals were far better in terms of being digitally equipped. A lot of changed have to be brought about in terms of government hospitals.

- One of the consumers believed nursing staff's behavior should be improved. More and more experienced nursing staff should be employed in hospitals.
- One of the consumers believed that hospitals should have more tie-ups with insurance companies to facilitate hassle-free payment.
- Cleanliness in government hospitals is still a concern.

Healthcare Provider Perspective:

A total of four persons who worked in the healthcare sector were interviewed in-depth.

Question 1:

- A health care professional working in the dental department usually said in a private hospital, the main technology adopted is cloud-based, which helps store the patient's records digitally, which provides a seamless experience for both the patients and doctors. The same cannot be said about government hospitals as they still store records manually.
- A healthcare worker (working in the administrative department) believed that government hospitals are still not digitally well equipped. They are skeptical about adopting new technologies. There is still a lack of infrastructure due to which the patients' experience could not be improved compared to private hospitals.
- A healthcare professional (General Physician) launched his app during COVID-19 to help patients in an emergency. The patients would describe their problems through the app, and accordingly, he would suggest proper diagnosis and upload the prescription.
- A healthcare professional (Oncologist) believed that introducing the latest technologies and equipment has helped treat cancers. Cutting-edge technology like cyclotron and PET-CT has been introduced; everything is cloud-based concerning storing patient information. The doctor has all the information regarding the patient even before the patient enters the doctor's cabin.

Question 2:

- A healthcare professional working in the dental department opined that the patients are aware of the cloud-based technology used in her organization to maintain patient records. She also mentioned that the records were protected using cybersecurity tools to prevent a data breach. In government hospitals (one in which she is associated), the patients are aware that their case papers are being stored.
- A healthcare worker (working in the Administrative department) said that this was out of government hospitals' scope.
- A healthcare professional (general physician) made sure that his patients were aware of his app; he sent a mailer to all his patients regarding the same.
- A healthcare professional (oncologist) said that since the cases of the patients that she handles are critical, each of the patients is made aware of the technologies used in their treatment.

Question 3:

- A health care professional working in the dental department felt that various factors influence any patient to choose a particular healthcare provider. Brand name of the provider, experience of the doctor, doctor's behavior, care beyond doctor's office, and digital readiness are factors.
- A healthcare worker (working in the administrative department) opined that other than doctor's behavior and care, factors like availability of good nursing staff and hospital infrastructure matter a lot to patients.
- A healthcare professional (General Physician) said that factors like the availability of doctors in need of the hour, shorter response time from healthcare providers, and word of mouth played a major role. Other than that, brand image and digital readiness were factors that influenced consumers to opt for a particular healthcare provider.
- A healthcare professional (Oncologist) believed that the most important factor in gaining patients' trust is maintaining transparency about their treatment. A doctor's behavior plays a major role in enhancing the consumer experience. In the technological aspect, patients will always prefer healthcare providers who are digitally well equipped to provide them with a seamless experience.

5. Conclusion

The study was undertaken to understand the various aspects affecting consumer behavior in the healthcare industry. The behavior of the consumers in the healthcare sector is quite different in comparison to other sectors. The study reveals that there are primarily five major factors influencing consumers in the healthcare industry: customer experience, digital readiness, brand image, word of mouth, and cost/expense. It can

be noted from the research analysis that consumers are slowly becoming aware of the adoption of technologies by their healthcare provider. The healthcare providers are also keeping pace with the technological advancements to enhance the consumer experience. They are trying to adopt advanced technologies like AI, big data analytics, augmented reality, etc., to better diagnose.

6. Limitations

The research paper's scope was limited to Indian consumers, so globally, consumers might have different points of view. The research was conducted mainly with consumers residing in urban areas; rural area consumers might have a different opinion regarding healthcare consumer behavior.

Scope of Future Research

The healthcare industry is adopting the latest technologies to enhance patients' experience. Advanced technologies such as augmented reality can benefit the healthcare industry by providing real-time access to patient data; it can also bring huge value to visualize health issues better. The future of research can be based on the adoption of advanced technologies in healthcare. Also, the scope of the study can be extended to consumers residing in rural areas. The parameters of the study can be extended to global consumers to gather their points of view.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Strategies for mitigating the effects of a pandemic on Indian medical tourism

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Abstract

India is a favorable destination for medical tourism because of its quality healthcare services and affordable treatment costs. It is a continuously growing industry across the globe. But whenever any pandemic situation arises, it adversely affects the industry. Currently, COVID-19 has a severe negative impact on the medical tourism sector. This paper discusses the effects of a pandemic, critical issues, SWOT analysis, and components that mitigate the adverse effects of pandemic diseases on medical tourism in India. During this phase, it is crucial to encourage domestic medical tourism for the sustainability of this sector. India's heritage of ancient medicine promotion, along with modern medicine can captivate the medical tourists. The destination country requires meeting the expectations of tourists through quality services. With India entering this unexpected downturn in this sector, destination country it must emphasize the slow and steady growth of medical tourism against the current and potential future pandemics.

Keywords

Medical tourism, Global market, Pandemic, SWOT, Inherent factors (AYUSH).

Imprint

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Introduction

In today's era of pleasure or business travel, medical tourism has created a new avenue for the healthcare industry in an innovative way[1]. The patients, as medical tourists, have the option of domestic and international travel to acquire the highest quality clinical expertise at affordable treatment costs. Based on the pattern of travel, medical tourism classifies as inbound, where a patient travels from a foreign country to the home country and intra-bound or domestic, where a patient travels within the country for medical treatment[2].

It is evident from the statistical data that 11 million people travel every year to seek medical care from their country, which is around 1% of the world's tourist volume[3]. Among tourists traveling for medical treatment, 95 % of patients travel for therapeutic or healing treatments, such as cardiac treatments, dental procedures, cosmetic surgeries, orthopaedic prosthesis, cancer treatments; and remaining to travel for wellness tourism, including rehabilitation, yoga therapy, stress reduction, and alternative medicine[4].

The global market for medical tourism was estimated at US$16.761 million and projected to grow to US$27.247.6 million by 2024, achieving a CAGR of 8.5 % by 2019-2023. Reports by FICCI and IMS Health India indicated that Indian medical tourism has nearly 18% of the international medical tourism market share[5]. As per the data of the Ministry of Tourism, the Indian medical tourism industry could be worth $9 billion, and it further estimated that Indian medical tourism would account for 20% of the international market share by 2020[6]. However, in 2020 due to a sudden outbreak of COVID-19, medical tourism has declined significantly due to lockdowns in most countries to reduce the spread of infectious disease[7]. Before COVID-19 world has experienced numerous pandemic outbreaks like severe acute respiratory syndrome outbreak (SARS) in the year 2002-2004, in 2009-2010 Swine flu pandemic, and 2012 Middle East respiratory syndrome (MERS)[8]. None of the past outbreaks declined the progression of the global tourism industry in the long term, except SARS and the current pandemic of COVID-19. The SARS affected global tourism by -0.4 %, whereas the COVID-19 affected more adversely with -44.4 % of the rate in the first four months of 2020[9]. Before the COVID-19 outbreak, the factors impacting medical tourism were modern technology, quality healthcare, visa accessibility, affordable cost, and very few efforts made for

considering the possible impact of the pandemic on medical tourism[10].

Accordingly, the present paper aims to study the factors affecting medical tourism and develop a SWOT analysis to foster strategies for mitigating the effects of a pandemic on Medical Tourism [11]. Further present paper aims to apprehend the impact of quotes such as "Health is wealth" and "Prevention is better than cure". Yoga, Ayurveda, and Indian ancient cultural practices more emphasized during COVID-19 for the growth of Indian wellness tourism[12].

Methodology

Descriptive research carried out for the study. The literature search was performed using the keywords: medical tourism, wellness, pandemic, and COVID-19. The studies presenting trends in medical tourism, the effect of the pandemic diseases, and the correlation between medical tourism and the pandemic have been taken into consideration. Data obtained from the relevant research papers and administrative records used for further review[13]. Information and the statistical data on the pandemic diseases are taken from the World Health Organization (WHO) and Centres for Disease Control and Prevention (CDC) website. Also, the tourist data obtained from the official website of the Ministry of Tourism India, Bureau of Immigration India, and Organization for Economic Cooperation and Development (OECD)[14].

Results

Global Medical Tourism Industry

The medical tourism industry is now promoted at a global level. Quality care and affordable health services are a principle phenomenon for the industry. Medical tourism analysts' claim that the international market for medical services enhance customer options, encourage competitiveness amid hospitals, and enable clients to access high-quality healthcare treatments across the globe[15]. Pessimists put up questions related to the quality service and safety of patients, confidentiality of patient records, legal action when patients harmed when providing hospital care in foreign countries, and damage to the national healthcare systems of the host country[16]. The development of a competitive global market for health services has important implications for health insurance, health service provision, and the expansion of consumerism in the healthcare industry. The serious threat to the expansion of the medical tourism sector is the pandemic diseases, especially when they are infectious such as currently COVID-19 pandemic[17].

As per World Health Organisation (WHO) report, around 215 countries and more than 20 million people have been infected with COVID-19 worldwide. It is an infectious disease that spreads through coming in direct contact with the infected patients and also by droplets from the contaminated surfaces. Preventive measures should remain more focused on reducing the spread of infection like keeping physical distance, self-isolation, and following proper sanitation methods[18]. As a result, the quotation of "prevention is better than cure" has been followed by most countries by imposing lockdowns and travel bans to reduce the spread of the disease. It stated that some countries restricted the entry of travellers from the affected areas and altered immigration rules; some have ordered the complete lockdown that no resident will travel to other nations. These restrictions and concerns of the disease have a major influence on the tourism sector and are anticipated to have a critical effect on medical tourism[19].

Even though many hospitals and clinics would have more patients and revenues increased by local clients but, the hospitals that are more dependent on international medical tourists strive for their finances. The hospitals must emphasize more on domestic medical tourists for providing quality care in this scenario[20]. In the hospital sector, the representation of quality services goes beyond the simple application of quality management to it as a whole. The implementation of quality improvement for medical tourism is very complicated as it entails individuals from different countries with diverse cultural backgrounds and needs. However, a healthcare organization can offer a wide range of services under one roof at an affordable price that can increase its revenue[21].

Medical Tourism Industry In India

In India, medical tourists travel from both developed and emerging countries. The patients travel from developed countries due to less waiting periods and affordable treatment costs and from the developing and underdeveloped countries because of the presence of the advanced healthcare provisions in India[22]. Reports show that India gives a competitive price benefit with one-tenth of the charge of Europe and the US.

Medical tourists also travel to India for wellness and alternative medicine like the AYUSH sector. Increased awareness related to the well-being of individual and alternative healthcare have enhanced the Indian wellness tourism.

Medical tourism is a complex and dynamic industry and therefore faces various challenges. There are following barriers/concerns for India as a tourist destination mainly for medical tourism:

- The perspective of International Patients as India has inadequate healthcare facilities, a lack of standardized processes, complicated visa procedures, and an unsanitary environment.
- The infectious pandemic diseases increase the uncertainty and apprehension among individuals, and this leads to the disruptive changes in medical tourism.
- There is still a shortfall of government initiatives, as there are no specific rules and regulations, variations in taxes, and lack of investor-friendly policies.
- Insurance related issues such as underdeveloped health insurance sector, fraud, and denial of reimbursement by international health insurance companies.
- Other challenges include quality accreditation of hospitals and laboratories, training and development of healthcare professionals, and a customer-oriented strategy.

SWOT analysis on Indian medical tourism

Strengths- India have affordable treatment costs. As per the American Medical Association study, the fees of therapy in India are almost three times lower than in western countries, such as the UK and the US. Qualified healthcare staff and advanced healthcare services including transplantation surgery and stem cell treatment are available. Many Indian hospitals and physicians have an international reputation. International students who come to India for their education can promote the Indian health services in their home country. India has its ancient wellness and medical strengths viz. Ayurveda, Unani, Yoga, Siddha.

Weaknesses- There is a shortfall of government initiatives and a regulatory system in India for medical tourism. Public healthcare funding is low in India as compared to other nations. Pricing strategies for different hospitals lack uniformity. There is less association between airlines, the hospitality sector, and the healthcare sector.

Opportunities- In particular, the awareness and demand for preventive health and wellness services are increasing globally. As India has its inherent strengths, this would be a great benefit for it. Developed countries have long waiting times so; countries like India can provide treatments in short waiting times. Emerging and underdeveloped nations have limited healthcare facilities so; India can deliver advanced healthcare treatments.

Threats- Healthcare professionals have a high brain drain. As per the Organization for Economic Cooperation and Development, nearly 69,000 physicians and 56,000 nurses worked in the UK, Australia, Canada, and the US in 2017 are Indian. Competition from other nations is increasing such, as Singapore and Japan. All health insurance companies do not provide coverage for international health services. Pandemic infectious diseases such as COVID-19 are currently a serious threat to the industry.

Medical Tourism and Economy

Medical tourism fosters direct foreign exchange earnings and raises the economy of the nation. It also empowers healthcare businesses and increases the job opportunities for the citizens. It enables the expansion of other related sectors, like pharmaceuticals, health insurance, tourism, wellness, and medical devices.

Currently, as a consequence of COVID-19, this industry has suffered significantly. Due to the lockdowns in most countries, tourist arrivals have dropped sharply, and foreign exchange earnings have therefore declined tremendously. The following graph shows the growth rate of international tourist arrivals and foreign exchange earnings through tourism. There is a significant reduction due to COVID-19.Figure 1 shows the growth rate of International Tourist Arrivals and the growth rate. It is, therefore, crucial to develop strategies to mitigate this impact at present and also to be ready for any future infectious pandemic diseases.

Components that mitigate the adverse effects of a pandemic on Indian medical tourism

The following suggestions set out India's potential path to take the lead in medical tourism.

Part of Government

1. As the airport is the starting point of contact, the facilities at the airport must be updated to take all

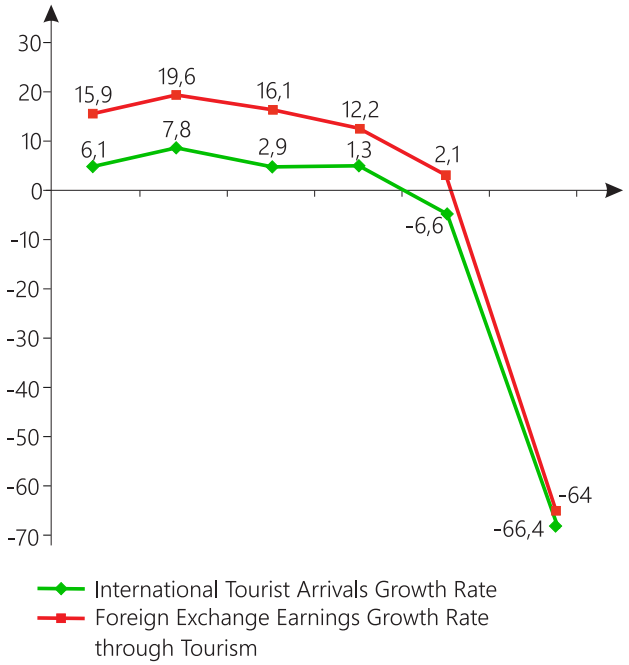

Figure 1. Graph showing the growth rate of International Tourist Arrivals and the growth rate of Foreign Exchange Earnings through Tourism (Oct'19-Mar'20)Data Source- Ministry of Tourism, India

the precautionary measures to obstruct the spread of the COVID-19 pandemic. The rapid test kits and thermal testing facilities must be available at all the airports. The authority must mandate physical distance travel in flights as part of the preventative measures. Tests were carried out for every suspected individual or traveller from the affected countries. All these preventive measures reduce the chance of spread of infection and also increase the credibility of the host country.

2. Digital connectivity needs to strengthen to provide extensive support for healthcare delivery. The use of telemedicine is encouraged to the extent possible for overseas patients. Clear guidelines for telemedicine must issue to all healthcare providers.
3. The medical visa process, the selection, and registration for healthcare services is challenging, so efforts should be made by the authority to make it simpler and less tedious by marketing and financially reinforcing the medical tourism companies. These help to captivate more international medical tourists and make India the leading medical tourist destination.
4. In addition to medical and surgical care, the emphasis should be on the preventive and wellness ancient practices of India like the AYUSH sector and naturopathy. These wellness practices boost the immunity of individuals and thus reduce the chances of infection. These not only prevent the current spread of disease but also certainly protect the individuals for any future infections. There should be the creation of holistic centres in healthcare providers such as the meditation room. This additional care services uplift the economy by increasing the revenues of the wellness industry.
5. Rules for health insurance companies relating to the provision of international insurance plans must consign. These should cover not only modern medicine but also the costs of digital consultations, wellness programs, and travel expenses.
6. The authority should set up a body to regulate medical tourism. These promote India's healthcare services through global marketing and also address the challenges of the international healthcare industry. The main agenda for such a body should be as follows:
   - Creating Indian Medical Tourism Brand in Abroad
   - Encouraging Inter-sectorial Collaboration
   - Information Circulation by Technology
   - Service Standardization
7. The Government may facilitate additional services, such as airline and hotel ties, the availability of translators, multi-cuisine kitchens, and leisure activities. These make the experience of patients much better and thus make India a leader in the medical tourism sector.

Role of Private Sector

To combat the rising competition and infectious pandemic diseases in the medical tourism market, private hospitals and laboratories in India must strictly follow international quality service standards such as Joint Commission International (JCI) Accreditation and College of American Pathology (CAP) Accreditation. Further emphases give to proper sanitation practices and to maintain physical distance at work. Web or application-based appointments and digital consultations should be facilitated as a prospective triage before the medical tourists arrive for treatment and follow-ups.

As a part of the marketing plan for various healthcare services, the tours and travel industries and healthcare providers can have packages, including transportation, lodging, and cost of treatment. They can carry out joint operations to improve medical

tourism. International institutions tie-ups promote medical tourism globally. It may be a joint venture between insurance companies or between hospitals. For additional revenues, other facilities of the wellness sector as meditation and yoga set up.

Currently, it is difficult to have international medical tourists due to the COVID-19 pandemic. So in such a situation, the private healthcare sector should focus on providing telemedicine to international patients. Also, emphasize more on domestic medical tourism and increase the awareness for ancient medicine and wellness systems to boost the immunity of the community.

Discussion

India is one of the fastest booming medical destinations around the globe; this is a novel model to improvise the existing medical tourism system by targeting international students in India. International students arrive from 164 nations around the world. According to the HRD Ministry report, the students in India enrolled for higher education are a total of 47,427 for the year 2018-19. Maximum international students arrive from proximate countries such as Nepal at 26.88 %, accompanied by Afghanistan at 9.8 %, Bangladesh at 4.38 %, Sudan at 4.02 %, Bhutan at 3.82 %, and Nigeria at 3.4 %. Therefore by establishing a novel Model that targets the International Students traveling to India for their education expands the scope of Medical Tourism.

The Model covers travel, accommodation, treatment, and post-treatment care. In the initial phase, the target is the International Students who travel to India for education and thereby slowly expanding and familiarizing the Global Market about the Model shown in Figure 2. Special concessions need to provide to the immediate family members of the students and referrals. The Model website includes details of treatment available and packages.

Ayurveda, Unani, yoga, naturopathy, and Siddha are another major inherent factor in India used to improve medical tourism. These systems of medicine focus not just on diseases but also the well-being of patients, their lifestyles, and the environment. These also help in boosting immunity, and in the current crisis, this can be a significant advantage to focus more on the Ayush sector. Ayurveda has been using natural herbs for the prevention and cure of diseases for thousands of years. It places more focus on prevention and promotes health conservation by proper attention to equilibrium in the right mindset and nutrition. Unani is a robust system that offers preventive and therapeutic health care. This system bases on scientific concepts and multidisciplinary ideas of wellness and cure. Yoga is the kind of practice offering mental and physical well-being to the individuals. It refreshes and detoxifies the system and strengthens the immune response of the body. Naturopathy focuses on balanced living and supports assisting the human body to eliminate disease causes. The Siddha system combines both spiritual and physical elements and treats the individual as a whole. All of these traditional health services need to take into consideration carefully to encourage domestic and international medical tourists and generate more revenues. India is known to have a rich heritage of the ancient medical and wellness system, and this attracts numerous foreigners to the country.

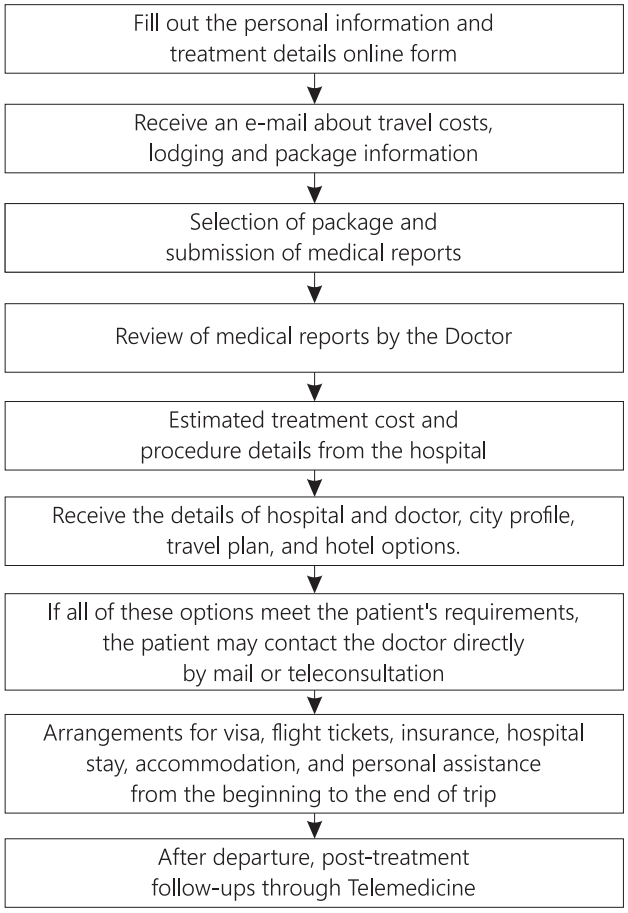

Figure 2. Process of the Model (Flowchart)

Conclusion

The medical tourism sector is a continuously developing and growing industry in India. But there are various obstacles experienced by the Indian medical

tourism industry, all the prospective to expand to number one position to attract international medical tourists, by working on its problems and improving service quality and maintaining it all the time. Pandemics such as COVID-19 are creating a significant shift in the medical tourism sector. Collectively, the goal is to learn from this global catastrophe and promote the transformation of the medical tourism industry. The part of the Government of India (GOI) is vital for the medical tourism growth. The government should take proposed measures and act as a board of control and enabler of private capital expenditure in healthcare. Since Medical Tourism is a combination of the healthcare and travel industry, both industries should enforce preventive measures comprising physical distancing and practicing sanitation. The use of telemedicine can help in strengthening the communication and information industries to reduce the contrary effects of COVID-19. Setting up the emerging board helps to reinforce and endorse medical tourism. Pandemic situations promote nationalism, so the medical tourism business should focus not only on international travel patients but also on domestic travel patients. Certainly, this way the medical tourism can further contribute to the country's economic development during this and any future pandemics.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REPORT

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Usage of nutritional supplements and its side effects among gym goers in Pune

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Abstract

Nutritional supplements have always been a point of attraction for physically active people. These have improved exercise performance, increased muscular strength, weight gain or weight loss, etc. The irrational use of supplements has led to various side effects associated with them. There is a shortage of evidence suggesting the usage and knowledge regarding the consumption of dietary supplements. A cross-sectional study was conducted with a 121 sample size randomly chosen from 5 different zones of the city. A structured questionnaire was designed to collect information wherein participants reported their demographics, physical activity, supplement usage patterns, source of information, and side effects. Descriptive statistics, chi-square test, was used with $p<0.05$ as significant. Samples used different dosages, forms, brands, and access to supplements. The participants coming to the gym for more extended periods were likely to consume supplements in higher dosages ($p = 0.020$). Protein powder was consumed by 97.5% of the samples. There was a significant association between different types of supplements across gender, age group, and period of exercising in the gym. Side effects such as cramps ($p = 0.015$) and nausea were significantly associated with high dosages of supplement consumption. The majority of them (51.2%) took advice from trainers. Only 9.9% consulted dieticians. Individuals consumed supplements without the guidance of any health professionals, which was predisposing them to various side effects. This reflects a lack of knowledge and awareness of supplement usage and highlights educating various stakeholders and gym-goers.

Keywords

Supplements, Nutrition, Knowledge, Side effects

Imprint

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Introduction

The supplement market has become a big business all over the world. Its consumption has increased up to 51% in the US. The estimates for 2016 include $41.1 billion in sales with 6% growth. The focus on living a healthy lifestyle, being physically fit is growing with time. This can be achieved easily through supplements. The ease in availability of supplements indicates the unreasonable population being reliable on dietary supplements, especially protein-based products reported by Global sports Nutrition Supplement Industry[1]. The amount of population searching for protein-rich food items has increased from 2006 to 2014 by 14%.

According to Dietary Supplement Health and Education Act (DSHEA), a dietary supplement includes one or more of the following ingredients: vitamin, mineral, herb or botanical, amino acids, concentrate, metabolite, constituent, and/or extracts[2]. The American Dietetic Association states that only individuals with poor dietary intake who are on severe dietary regimes or eliminate few foods items from their diets may require supplementation. Despite these guidelines, the usage of supplements is high in both athletes and people who exercise daily[3].

Survey results have shown that dietary supplements have been taken for various advantages related to exercise, physical, mental strength, immunity, treating diseases, or health-related issues.) In short, they give “miraculous” or “magical” results, which attract consumers[4]. In addition to these advantages, there is also much influence by media and the role models for better physic. The users constantly contact advertisements in glossy magazines and on the internet, which has led to increased consumption of dietary supplements[5].

The reasons for consumption have been attributed earlier; however, the usage of supplements is not devoid of potential hazards. There are still various misconceptions regarding the use of dietary supplements among individuals[6]. The irrational use of nutritional supplements carries several health risks; hypertensive reaction, gastrointestinal disturbance, depression.

Nevertheless, consumption of supplements in gym-goers has been high irrespective of its side effects [7]. This can be attributed to the lack of knowledge about the requirements, the amounts to be consumed, and their actual use. The quality control ensuring the supplements to be safe, containing no adulterated or banned substances depends upon the manufacturers of the supplements[8]. There are no strict regulations for it, neither are they well documented.

Lately, India has also witnessed a surge in the number of people attending gyms and fitness centers for achieving a healthy and fit lifestyle[9]. There have been gyms at every corner, and more young adults are following such practices. In recent years, along with an increase in the global market, individual spending capacity has also increased[10]. Thus, people are spending more on supplements. Differences in supplement consumption exist depending upon age, gender, source of information, and aim of exercising. Unfortunately, there is a dearth of evidence suggesting usage and awareness about dietary supplements among the population. Thus, the study on nutritional supplement consumption among gym-goers will bring to light a great deal of information about a topic that has not been researched in this part of the country[11].

Material and Methods

The present study was a cross-sectional study conducted in the city of Pune. The study was approved by the Institute Research Committee (IRC) of Symbiosis School of Biological Sciences (SSBS), and approval by the Independent Ethical Committee (IEC) of Symbiosis International Deemed University was obtained.

Selection of samples

The participants taken from 10 different gyms were of both genders from age 18-40 years. The inclusion criteria were: the participants should come to the gym at least four times a week and consuming any of the supplements. Athletes, sports persons, trainers, and health professionals were excluded from the samples. A random sampling method was used to enroll the participants.

The gym-goers were approached, considering the inclusion and exclusion criteria in mind, and explained thoroughly about the study. A short introduction of the researcher was given in the beginning to each participant[12]. The study objective was explained through the subject information sheet and in–person. The subjects were then provided with informed consent, those who voluntarily agreed to participate in the study.

Selection of gyms

The participants were collected from the gyms situated in the different areas of Pune. A map of the city was taken and divided into five different geographic locations (North, East, South, West, and Central). The selection of gyms was random and as per the permissions given. Before the commencement of the study, official permissions were taken from different gyms. The managers or floor-in-charge were contacted for permission[13] [29]. Later on, senior authorities were approached for the permissions. Those who granted them permission to collect the data were included in the study.

Sample Size

The sample size was calculated considering 95% level of significance, 84% proportion of picking a choice, and 0.05 as the degree of precision. The estimated sample size was n = 246, but due to personal reasons, those who withdrew or could not complete the questionnaire; the data was then available for 121 participants[14].

Questionnaire

A structured self-designed questionnaire included domains regarding the demographics, physical activity, supplements use, and side effects. Questions concerning age, gender, educational qualifications, income came under the demographic characteristics of the participants. The type, frequency, and purpose of exercising, time since they started coming to the gym, and hours spent per day at the gym were also included[15]. Lastly, it included types, dosage, and frequency, source of information, access, and side effects of supplement consumption. A pilot study was conducted to check the efficacy of the questionnaire in 4 different gyms for 30 participants[16].

The limitations were corrected, and a final questionnaire consisting above domains was used for the main study. The data was collected via an interview method involving one-to-one interaction with the participants. The researcher was present while filling the questionnaire to provide help. At a time, two people were approached. Each participant required 10 – 15 minutes to fill the questionnaire. In the end, the questionnaire

was checked by the researcher, and missing details were filled in to avoid inconsistencies [17] [20].

Statistical Analysis

Statistical analysis was done by SPSS software (version 20). The normality of data was tested using the Shapiro Wilk test, and Z scores for skewness and kurtosis within ± 2.58 with the $p < 0.05$ were checked[18]. The data was first entered into excel and then in SPSS to avoid errors. The variables were categorical and appropriate codes were assigned to them[30]. Descriptive statistics were used for identifying percentages, frequencies, and standard deviations of demographic characteristics, supplement usage, and side effects. A Chi-square test was used to identify associations for supplement usage across gender, age group, and physical activity. The significance level was considered at <0.05[19].

Results

Demographic characteristic

The socio-demographic characteristics of the participants are shown in Table 1. Of 121 samples, 96 % were men. The participants mostly consisted of young individuals, with 44.6% falling in the age group 18-25 years. All the samples were literate. Most of them were graduates (55.4%), while some were having higher professional degrees (35%). Only 7.5% were at the high school level[21].

Substance abuse

As shown in Table 1, 49.6 % of the supplement users consumed alcohol. This was significantly associated. ($p = 0.039$). Out of which 38% reported that they drank only once a week that too on weekends. Most participants (68.6%) were non-smokers. Out of the ones who smoked, the majority (24%) smoked 1 – 2 cigarettes a day[22].

Physical Activity

The types of exercises performed by the participants are shown in Table 1. Also, the time since they were exercising in the gyms has been depicted[23]. Out of all the participants, 56.2% performed strength exercises, 9% performed balancing postures, and 33.1% performed a combination of strength, balancing, endurance, and flexibility exercises[24]. The time spent by the participants at the gym varied: 59% of individ-

Table 1

Demographics, types of physical activity, and supplement usage of the participants

Variables	Percentage of participants (n)
Gender	
Male	79.3(96)
Female	20.7(25)
Age	
18-25	44.6(54)
26-33	38(40)
>33	17.4(27)
Alcohol	
Yes	49.6(60)
No	50.4(61)
Smoking	
Yes	31.4(38)
No	68.6(83)
Qualifications	
Profession or honors	28.9(35)
Graduate	55.4(67)
Intermediate or diploma	8.3(10)
High school certificate	5.8(7)
Middle school certificate	1.7(2)
Type	
Strength exercises	56.2(68)
Balance exercises	7.4(9)
Aerobic/Endurance exercises	1.7(2)
Flexibility exercises	1.7(2)
Combination	33.1(40)
Time Period	
1 – 3 months	17.4(21)
3 – 6 months	14.0(17)
6 – 12 months	16.5(20)
>1 year	52.1(63)
Aim	
Health and fitness	47.9(58)
Muscle growth	33.1(40)
Weight gain/Weight loss	15.7(29)
Improvement in performance	8(1)
Fitness and muscle growth	2.5(3)
Continued	
Continuation	
Duration (in hours)	
1	48.8(59)
2	45.5(55)
3	5.0(6)
4	0.8(1)
Dosage of supplements	
20 – 40gms	54.5(66)
40 – 60 gms	33.9(41)
60 – 80 gms	5.8(7)
>80 gms	5.8(7)
Duration of consumption	
Quarterly	38.8(47)
Half-yearly	16.5(20)
Yearly	3.1(11)
More than one year	35.5(43)
Form of supplements	
Powder	81(98)
Capsules	2.5(3)
Pills, powder, and capsules	7.4(9)
Powders and pills	5.0(6)
Powders, pills, capsules, and drinks	4.1(5)

uals spent 1 hour at the gym, and 55% spent 2 hours. The participants who were coming to the gym for more than one year comprised 52%[25]. They joined the gym for the following reasons: health and fitness (47.9%), muscle growth (33.1 %), and weight gain or weight loss (15.7%) which was significant. (Table 2)

Table 2

The reason for exercising in the participants consuming supplements by gender

Aim	Percentage of supplement users		Chi-square value (χ^2)
	Male %(n)	Female %(n)	
Health and fitness	42.7 %(41)	68%(17)	8.286*
Muscle growth	38.5%(37)	12%(3)	
Weight gain/weight loss	14.6(14)	20%(5)	
Health and Muscle growth	4.2% (4)	0%(0)	

*p = <0.05

Use of Supplements

The participants in the study reported a total of 13 products that were used as supplements in one form or another [26]. The list of the type of supplements consumed is given in Table 3. The five most common types of supplements consumed were: Protein powders (97.5%), Branched-chain amino acids (43%), Multivitamins (32%), Antioxidants (27.3%), and B- complex (16.5%), as shown in Figure 1. Men consumed more amounts of supplements than women. The majority of the participants consumed 20-40 gms of supplements (54.5%). The powder form of supplements was majorly n = 98(81) used, as shown in Table 1. Others took a combination of powders, pills, capsules, and sports/ energy drinks. Multiple brand choices were found among the participants [27]. Almost half of the population spent 1 – 5 k on the supplements. Only a few were spending more than 20 k per month (data not shown). 39% of the individuals started consuming supplements in the initial three months of joining the gym [28]. Thus, Table 4 depicts that individuals who exercised in the gym for longer time periods tend to consume supplements and that too in higher dosages. ($\chi2$= 58.621, p = 0.000; $\chi2$ = 26.810, p = 0.002)

Supplement consumption on the basis of gender

Men took more supplements than women (Table 5). None of the women reported consuming glutamine

Table 3

Different categories of supplements used by the participants

Antioxidants- Vitamin C,E	ZINC
Beta-Alanine	Coenzyme Q10
Chromium	Creatine
Tyrosine	Ephedra
Glutamine	L- Arginine
L- creatine	Melatonin
Multivitamin	Question
Anabolic Compounds	Sports drinks
Sports gels	Energy Drinks
B complex	Protein bars
BCAA	Protein powders

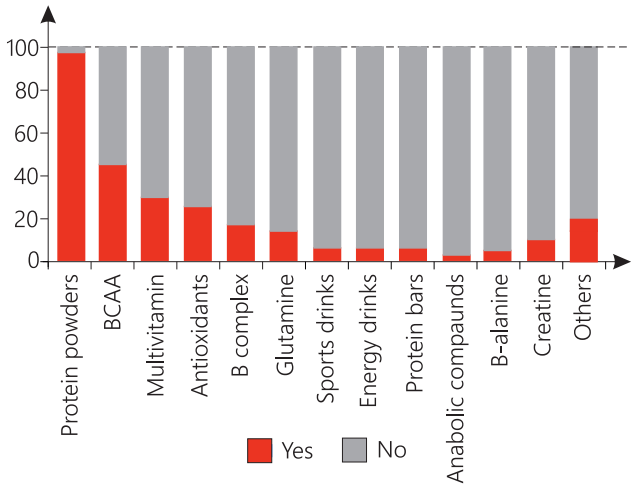

Figure 1. Different types of supplements were reported by the participants

(p = 0.023) since it is involved in muscle growth which is the aim of the male population. Similarly, BCAA was consumed mostly by men (52.1%). Only 8% of women reported consuming BCAA. (p = 0.000) Though there wasn't a significant association found in the consumption of protein powders, multivitamins, and others, their consumption was higher in men than women.

Supplement consumption on the basis of age groups

The association of supplement usage amidst different age groups is shown in Table 5. For comparative reasons, the age group was divided into 18-25, 26-33, and >33 years old. It was found out that supplements were mostly consumed by the younger participants. (18 – 25 years). Among all the supplements, B- complex (p = 0.020), BCAA (p =0.042) was significantly associated with age group.

Table 4

The dosage and time period of consumption of the participants with their period of exercising in the gym

Time since started exercising (in months)	Time since they are consuming supplements (in months)				Chi-Square (χ2)	Dosage of supplements consumed (in gms)				Chi-Square (χ2)
	<3	< 6	< 12	>12		20 – 40	40 – 60	60 – 80	>80	
1 – 3 % (n)	34 (16)	15 (3)	9.1 (1)	2.3 (1)	58.621*	80.9 (38)	17 (8)	2.1 (1)	0 (0)	26.810*
3 – 6 % (n)	25.2 (12)	25 (5)	0 (0)	0 (0)		40 (8)	50 (10)	5 (1)	5 (1)	
6 – 12 % (n)	21.3 (10)	20 (4)	36.4 (4)	4.7 (2)		36 (4)	54.5 (6)	0 (0)	9.1 (1)	

*p = <0.05

Table 5

Consumption of different types of supplements with respect to gender and age*p = <0.05, **p = <0.01

Type of supplement	Gender		Chi-square value (χ2)	Age group (in years)			Chi-square value (χ2)
	Male	Female		18- 25	26 – 33	>33	
Glutamine Yes No % (n)	17.7(17) 82.3(79)	0(0) 25(100)	5.151*	47.1(8) 44.2(46)	35.3(6) 38.5(40)	17.6(3) 17.3(18)	0.066
BCAA Yes No % (n)	52.1(50) 47.9(46)	8(2) 92(23)	15.729**	32.7(17) 53.6(37)	50(26) 29(20)	17.3(9) 17.4(12)	6.356*
Protein Powder Yes No % (n)	96.9(93) 3.1(3)	100(25) 0(0)	0.801	45.8(54) 0(0)	36.6(37) 3(100)	17.8(21) 0(0)	5.016
B- complex Yes No % (n)	16.7(16) 83.3(80)	16(4) 84(21)	0.006	20(4) 49.5(50)	45(9) 36.6(37)	35(7) 13.9(14)	7.862*
Multivitamin Yes No % (n)	35.4(34) 64.6(62)	20(5) 80(20)	2.158	25.9(14) 74.1(40)	42.5(17) 57.5(23)	29.6(8) 70.4(19)	2.998

Access to supplements

The access to supplements was majorly n = 68(57) through stores. The rest of them preferred either gyms (15.7%) or online (18.2%) or medical shops (3.3%). It is evident from Figure 2 that medical shops were the last chosen option to buy supplements.

Source of supplement information

Half of the population (51.2%) took advice from trainers before taking supplements (Figure 3). Unfortunately, only a small percentage (9.9%) took professional advice from dieticians. The participants also self-prescribed themselves (22.3%). Uncertain and convenient sources such as friends, family, or fellow

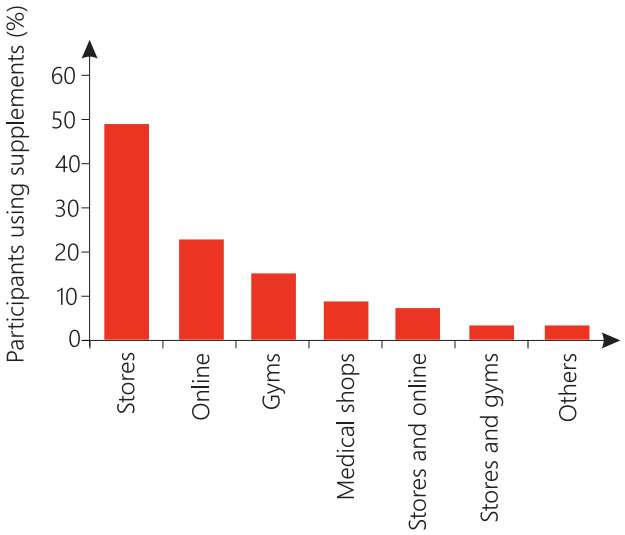

Figure 2. Access to supplements

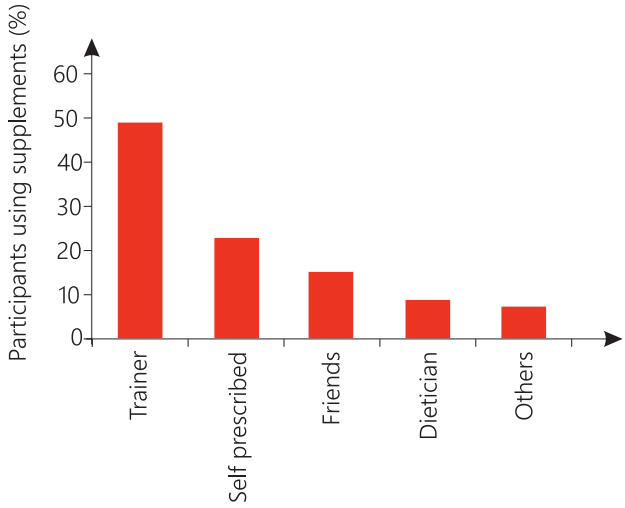

Figure 3. Source of information among supplement users

mates (12.4%) were also the source of information for the participants.

Side effects

The side effects (Figure 4) associated with the use of supplements were reported by the participants. The side effects reported were abdominal pain, abdominal bloating, cramps (p=0.015), nausea (p = 0.087), Vomiting, headache, dizziness, feeling of fullness, and few others. However, the majority of them did not experience any side effects or said that the use of supplements did not have any.

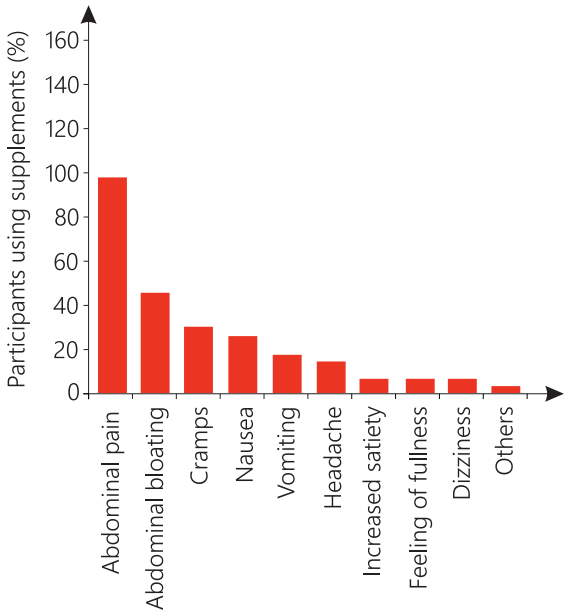

Figure 4. The percentage of participants experiencing any of the side effects

Discussions

The objective of the study is to find the intake of nutritional supplements among the people exercising in the gym. This is one of the first studies done in this area of the country. There is scanty information available on the patterns, usage, and consumption of the supplements, especially in India. There are studies published worldwide in this domain (Khoury, 2012; Morrison, 2004; Lacerda, 2015; Saleh, 2015; Alshammari, 2017; Goston, 2010; Attlee, 2018, Bianco, 2011, 2014). However, most of the studies on supplement usage focus on the athletic or sports individuals who form the major percentage of it (Knapik, 2016; Aljaloud, 2013; Wilson, 2016; Rockwell, 2001; Huang, 2006). The requirement of the body is increased due to high-intensity physical activities done in various sports; thereafter, the metabolic requirements also increase. Hence, this constitutes the foremost category of supplement users. Another important category of supplement users is Gym goers. Few studies conducted in other parts of the country focus on a similar theme (Malik, 2010; Karthik, 2017).

In the present study, several gyms were approached from 5 zones of the city, and those who voluntarily agreed were enrolled in the study. Socio-demographic characteristics of the participants were calculated using the Kuppuswamy scale, which included details about their age, gender, educational qualifications, income, and substance abuse. The present study population consuming supplements was more with a degree of graduates or diploma. There are similar findings from a study done in Brazil wherein the participants at least held a high school certificate or were college graduates. Another study done in the same locale showed 69.9% of participants had completed their high school. Socioeconomic status is also a factor of supplement consumption among individuals. Population belonging to low socioeconomic status tends to compromise on the quality of supplements and food. On the other hand, high socioeconomic class people have a greater purchasing capacity to buy good quality products.

The BMI score (WHO, 2004) fell in the normal range for the majority of the participants. The probable reason for this can be health consciousness and the period since they are into exercising. The aim of females found in other studies included fitness, toning their body, general health benefits, while the males were more interested in leaner bodies, muscle growth, bodybuilding, and enhancement in performance. Similar results were found in this study wherein females (68%) were more diverted towards health and

fitness, and males (37%) were interested in muscle growth and improvement in performance. The results were statistically significant. ($\chi 2=8.286$, $p = 0.040$)

Supplement consumption patterns differ by gender, age, purpose, and duration of exercise. It has been consistently shown that the male population tends to consume more supplements than the female population. The present study found the consumption of Glutamine, BCAA in male participants. Glutamine has a role in the oxidative metabolism of the body. Its supplementation leads to an increase in VO_2 response time and an increase in muscle oxygen uptake. It also preserves phosphocreatine and glycogen in the fibers of the muscle, which depicts its role in aerobic exercises. These types of results reflect the use of these supplements in bodybuilding or muscle growth, hence more commonly consumed by males. Other supplements did not correlate with gender. On the contrary, studies prove the consumption of protein powders is higher in males while consumption of vitamins and minerals is higher in females. This is due to the effects they produce on the bodies. Many investigators have reported that protein is the most used ergogenic supplement. This is clear because of its role in muscle building and other metabolic mechanisms. The present study also found out that the consumption of protein powders by 97% of the participants but was not statistically significant, possibly due to the small sample size. It has been suggested that the requirements of protein increase either in special circumstances or for athletes. Individuals who exercise regularly can easily fulfill their requirements by consuming wholesome, nutritious meals or following a well-balanced diet. There is no requirement for supplementation in such populations.

The percentage of supplement consumption was found higher in younger age groups than older adults. There are similar findings in the present study as well. Other studies like one done in Belo Horizonte also showed higher percentages amidst the population younger than 30.

Anabolic steroids have been relatively used by athletes in sports. Studies reveal that they have an effect on protein synthesis in muscles and neural changes in the brain. The results are contradictory. In the current study, only two subjects reported consuming these. There can be under-reporting of this. Generally, people do not openly report regarding anabolic steroids or about their diets. This study did not find a significant association of consumption of antioxidants and multivitamins within respective age groups. This is contradictory to other studies which got a significant association of antioxidants, natural supplements, and protein powders to the age group of 20 – 30 years. In another study, it was proved that multivitamins and mineral supplements are consumed more in the older population than younger ones.

The participants who have been exercising for a longer duration tend to consume supplements in higher dosages (Table 4). This can be due to increased interest in a healthy body, sports activities, to be in that environment for a longer duration which has a greater impact on one's mind. Moreover, the trainers, coaches, and fellows with good bodies influence them to consume supplements. This study highlights those findings wherein the participants (34%) are found to start consuming supplements immediately the time they join the gym.

As the period of exercising in the gym increases, the dosage of the supplement also increases (Table 4). This can probably be because of a plateau that is attained in the body. To break the plateau, individuals tend to consume more supplements to get the leaner cuts or increase the muscle mass in the body. The individuals opt for supplements since they feel they are experienced enough now and linger for better bodies which resort them to consume dietary supplements. Also, long durations of exercise lead to increased muscle hypertrophy, which cannot be attributed to supplement use by the population. Another study by Sao Paulo found a similar association with periods of exercising and increasing supplement use.

European Journal of sports mentions the scientific researches stating that people belonging to different locations, different backgrounds have varied opinions about supplements and proper dietary habits. This can also be due to underreporting or over-reporting by the individuals.

In spite of people being aware of the potential side effects caused by supplement consumption, people continue to consume them. The results from various studies reflect that a greater percentage of people were unaware of side effects caused by supplement consumption. Consumption of high doses of supplements can cause potential adverse outcomes. In spite of knowing such outcomes, people continue to consume supplements in the illusion of "magical" results they produce. The participants in the study reported various self-perceived side effects. Maximum numbers of

individuals are not aware of the adverse side effects of excess consumption of supplements. They primarily report digestive issues and are not aware of long-term side effects.

The media have been quite influential in the supplement industry. The advertisements put upon such platforms have a major impact on the population. Internet and self-prescribed supplements accounted for a major percentage. Guston reported 55% of participants consumed supplements without any guidance from health professionals. Only 12.8% consulted dieticians before taking supplements. Other sources like magazines, posters, pamphlets, advertisements, friends, the family were considered as major sources. A study by Bianco in Italy in 2011 showed that fitness instructors were a major source (37%) of information for gym-goers. Individuals do not consult any health professional regarding the information of supplements. Either they self-prescribe or consult their trainers or coaches.

The present study shows half of the participants consulted their trainers. Only a small percentage consulted dieticians before consuming supplements. The reason for this could be the extra money they have to put in to consult a dietician. Apart from that, people also have to invest more time in such consultations. It takes a longer time to get those results which they get easily from supplements in a very short duration of time. It was found out that the participants had incomplete knowledge about nutrients found in foods. They researched on Google and start following it without any scientific evidence or guidance from health professionals.

Conclusion

In conclusion, Supplements have long been appealing to athletes. Also known to enhance workout performance, muscle strength, weight growth, or loss. The irrational usage of supplements has caused numerous adverse effects. There is a lack of research and understanding about dietary supplements. Cross-sectional research was performed with 121 randomly selected participants from 5 distinct metropolitan zones. A good number of people who exercise regularly at gyms consume dietary supplements without taking any professional expertise. Due to lack of data, the long-term side effects of over intake of supplements are not known. Supplementation must be given in cases of poor diets or diseased conditions, which is possibly not the case with gym-goers. Irrational use of supplements can lead to various health-related problems. Also, these over-the-counter drugs are easily available in the markets, which poses a serious concern in their regulation. Hence the study reflects upon the irrational use of supplements and recommends further researches in the same area to generate relevant data from the entire country to channelize the sale of supplements.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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REVIEW

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Hedonic hunger: eating for desire and not calories

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Abstract

Hedonic hunger can be described as a state where an individual experiences recurrent feelings, thoughts, and desires about food in the absence of energy deprivation. Living in an obesogenic environment where cheap, tasty foods are available in plentiful amounts is one of the major causes of hedonic hunger development. Hedonic hunger can be analyzed using a power of food scale (PFS) which estimates appetite and not palatable food consumption. The current epidemic of obesity globally (termed as "globesity" by WHO) is seen to be majorly driven by the hedonic eating system and an imbalance in the energy homeostasis system. Previous studies indicate that hedonic hunger and obesity are associated, and a weak but no significant correlation exists between BMI and PFS score. It can lead to the development of various lifestyle disorders in the longer run. High levels of pleasure-driven hunger can even lead to detrimental health outcomes like poor glycaemic control, unhealthy dietary behavior, and increased lipid profile levels which are aggravated explicitly in cardiovascular diseases. With the adaptation to western dietary lifestyle, people are keener to opt for food options that can be damaging and harmful when low levels of self-control, dietary motivation, and healthy dietary habits are absent. Apart from the reward regulation system, which has a direct effect on hedonic hunger, certain external factors like emotional eating, meals and meal preparation, food cravings, sleep, physical activity, stress, social media, portion size, peer influence, an atmosphere of a restaurant can also promote more than required intake of food. This review article summarizes the above findings taking into account the plethora of research studies conducted so far.

Keywords

Hedonic hunger, Reward, Obesogenic environment, Obesity, Palatable foods, Food intake

Imprint

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Introduction

The term hedonic hunger can be described as "one's preoccupation with foods and the urge to consume them for the sake of pleasure and in the absence of physical hunger." Since ancient times the primary motive behind eating was to survive by maintaining the energy homeostasis levels and avoiding starvation. Due to the transition of changing lifestyle, unhealthy dietary habits, and the presence of an obesogenic environment, most of the food consumption in today's world occurs for reasons other than energy deprivation [1]. Food is one of the intense pleasures in life. The growing ratio of food consumption in humans is stimulated by delight and not the need for energy-giving calories giving rise to "non – homeostatic" eating or "hunger for pleasure." In a food-abundant environment characterized by a large number of low cost, readily available, and palatable, energy-dense foods, which are always universal, it is possible that hedonic hunger can affect eating patterns over homeostatic eating activity[2]. The psychobiological system usually consists of homeostatic and hedonic characteristics of hunger which work mutually and affect food consumption[3]. The homeostatic pathway controls the energy balance and is coordinated by the hypothalamus; it responds to the inner signs of energy requirement and incentive to eat when there is depletion in energy levels[4]. In comparison, the hedonic eating pathway weakens homeostatic regulation throughout ample energy, and there is an inclination towards eating more delicious foods. Neurobiological studies conducted in both humans and animals show that when a flavorsome food commonly high in fat/salt/sugar is consumed, it increases the activation in the reward-related areas in the brain, which in turn causes the release of dopamine[5]. The levels of dopamine secreted are related to the feeling of happiness that is obtained after consuming it. According to Stice, sometimes, the oral, sensory, and gustatory properties of palatable foods such as smell the taste can also induce dopamine release[6].

The influential theory of reward suggests that it is a distinct procedure that considers a pleasure com-

ponent and a non – pleasure component that can be termed as "liking" and "wanting." Enjoying food is subjective to the delight obtained from it, and desiring it is the motivational bit of reward, and its related environmental indication is also called "incentive salience attribution"[7]. However, it has been suggested that recent development in the research area should emphasize more on the difference between "liking" (pleasure-based eating) and "wanting" (incentive to indulge in eating) and its relation to behaviors of consumption of foods in humans[8]. The hedonic eating system seems to be independent of the homeostatic pathway. It plays a vital role in eating behavior by increasing the desire to eat, inhibiting the signs of fullness, and ultimately leading to high energy-dense foods[9].

Studies previously aimed at differentiating hedonic versus homeostatic hunger showed that the palatability of food is highly associated with hedonic hunger due to its rewarding properties even when there is no energy deficit. Combining an environment filled with highly palatable foods makes it more "psychologically available" for consumption, leading to widespread hedonic hunger [10]. Hedonic hunger can be analyzed using a power of food scale (PFS) which estimates appetite and not than palatable food consumption and consists of three domains which include the availability of food, presence of food, and how the food tastes and it is now considered as a new measure of appetite[11].

This review article aims to elaborate briefly and summarize the extensive research studies conducted on hedonic hunger so far and look into various other aspects. Existing literature enumerates hedonic hunger's role in developing obesity, different long-term and short-term health effects linked with hedonic hunger, and its impact on eating behavior [12]. Few studies have also tried to analyze the role of self-regulation or self-control on hedonic hunger and various factors which can influence or affect hedonic hunger scores. Most of the studies have considered the western population, and robust research in the Indian population is still missing[13].

Hedonic hunger and its association with obesity

The prevalence of obese and overweight individuals globally is around 1.9 billion and 650 million individuals, respectively. The current epidemic of obesity stems from an imbalance between the modern lifestyle/environment which includes unhealthy dietary habits (consumption of energy-dense foods), sedentary lifestyle, and inner attributes like strong attraction towards foods and food signals, delayed mechanism of fullness, and increased metabolism rate[14]. The development of obesity is the outcome of gene-environmental interaction, controlled by neuronal and hormonal systems, and overeating plays a dominant role in obesity. It activates regular intake of tasty and calorie-rich foods when no physical hunger is present. The constant accessibility of such highly delicious foods inhibits the dopamine reward circuit in the brain both oral and after the food is ingested[15].

Accumulating evidence establishes a clear link between obesity and the brain reward activation system. Obese compared with normal-weight individuals show a more significant response to the anticipated food intake than actual food intake. Regions in the brains responsible for food coding sensory and hedonic properties include gustatory and somatosensory areas [16]. There is greater activation in these regions in response to predicted food intake and consumption. Still, there is delayed activation in the striatum region of the brain throughout food intake, which increases the chances for overeating leading to frequent gain in weight. A similar observation was found, which also showed decreased dopamine receptor activity which can predispose them to excessive food intake. Animal studies also suggest that repeated or excessive consumption of sweets and foods rich in fat can cause reduced activity of Dopamine receptors and a reduction in sensitivity towards dopamine receptors [17].

A measurable component of hedonic hunger that is the sensitivity to palatable foods and their rewarding properties, can is assessed by the power of food scale (PFS) forms a crucial element for identifying the association of BMI with Hedonic hunger. BMI, in turn, represents the nutritional status in terms of obese and overweight individuals. A weak and not statistically significant association between PFS score and BMI was observed in a clinical study conducted. For overweight & obese individuals, the PFS score might be related to overeating tendencies compared to BMI. Findings indicated that severely obese patients without a history of gastric bypass surgery had higher PFS scores. There was an apparent increase in their levels of hedonic hunger compared to patients who underwent gastric bypass surgery earlier. Obese individuals with a history of gastric bypass surgery or bariatric

surgery exhibit low levels of hedonic hunger compared to patients with a history of gastric bypass or bariatric surgery. Specific obesity-related eating behaviors like selective observation to food signals, food cravings, eating disorders like binge eating with self-administered overeating were also observed with high hedonic hunger levels. Individuals with higher PFS scores have increased chances to develop loss of control (LOC) overeating for both normal BMI populations and obese BMI populations. In a study conducted among women, hedonic hunger score was found to be high in obese women compared to non-obese women.

In agreement with previous data, a study also showed no significant correlation between P-PFS score and BMI in obese and healthy weight individuals. Various other authors have demonstrated a similar lack of correlation in specific samples of young adults, young adult women, healthy students, obese and overweight women[18]. However, a weak positive correlation was seen when both the samples were merged. This association mainly resulted because of significant group dissimilarity in PFS score among obese and normal-weight patients. Among the three categories in the power of food scale, the PFS score for food availability is strongly associated with the development of obesity. In contrast, the PFS score for the taste of food had a minute or no relation. With each unit increase In the P-PFS score for food availability, the chances of being obese increase approximately two times.

Effect of hedonic hunger on eating behaviour

Hedonic hunger is linked with maladaptive eating behavior, including frequently consuming more significant portions of food, eating unhealthy foods between regular meals, and eating when not hungry. Pleasure-driven hunger can be both desirable and dangerous. Today's obesogenic environment provides foods that are palatable, cheap, and accessible and has the power to stimulate hedonic appetite on their own. Edible foods refer to foods that are acceptable by the palate or taste buds. They are energy-dense and are primarily rich in fat and sugar or both[19]. The consequent weight gain linked with the rewarding properties of flavourful foods, which are rich in fat and sugar, predisposes the risk for developing obesity, hypertension, diabetes, gallbladder disease, and cardiovascular problems. Increased consumption of fast foods also has a role to play with metabolic syndrome in children and adolescents. Hedonic hunger is seen to be more prevalent in females than males, but on the contrary, when choosing a food, they tend to focus more on health-based aspects of the food rather than taste compared to males. Younger adolescents are less worried about health and more bent towards how a particular food tastes.

Studies have shown that people having high levels of hedonic hunger have more excellent processing in the optic areas of the brain when both words and pictures representing highly palatable foods are shown to them. When presented with options, they are more likely to select unhealthy snack foods. Research conducted illustrated that high levels of hedonic hunger can be one of the causes of unhealthy dietary behaviors. Centrally obese people suffering from type 2 diabetes mellitus had unfavorable cardiometabolic findings, high levels of pleasure based hunger and harmful nutritional habits, including irregular meal patterns and diet, frequent intake of sweet foods like pastry, desserts, etc. Hedonic hunger also has an independent and inverse relationship with glycaemic control, and obese individuals with type 2 diabetes had high levels of hedonic hunger. A significant positive relation between hedonic hunger and glycaemic power was noted.

According to[20], individuals tend to eat for the sake of happiness and delight and not to meet the nutritional intake. Hedonic behavior can mislead the consumers when choosing foods because they cannot control their nutrient intake when consuming foods and are not ready to compromise on their taste buds for health. On examining the association between hedonic hunger, health interest on habit, and sodium intake, it was found that pleasure-driven need and health interest affect practice. Still, no impact on sodium input was seen because of the tendency to eat for taste; there was no control on the salt intake, leading to ignoring health and nutritional aspects like the development of hypertension in the future.

There is growing evidence among clinical and non-clinical samples that high levels of hedonic hunger can lead to losing control over overeating, which can be an essential feature of binge eating and gaining weight. No proper evidence exists on the relationship between eating disorders and hedonic hunger among individuals. Results from a study conducted revealed that individuals suffering from bulimia nervosa (BN) scored remarkably increased levels of hedonic hunger when compared to individuals suffering from oth-

er eating disorders like a restrictive type of anorexia nervosa, binge, or purging type of anorexia nervosa, and individuals only suffering from anorexia nervosa. It can also be assumed that notable weight gain among individuals with anorexia nervosa (AN). These findings remained consistent even after adjusting for restrained eating or suppression of weight. More evidence is needed to establish a strong correlation between hedonic hunger and eating disorders.

Role of self-regulation and motivation on hedonic hunger

Self-control is one of the crucial predictors for hedonic hunger. Despite living in a food-scarce environment, health-conscious individuals tend to maintain their weight throughout and are not affected by the high availability of flavorsome and tasty foods in their surroundings. People with increased levels of inhibitory control depict lesser stories of overeating, snacking frequency, and less intake of unhealthy snacks compared to the population with decreased levels of self-control. However, findings indicate that individuals with insufficient or low levels of inhibitory control are susceptible to overeating and unhealthy snacking when palatable food cues are present[21]. The activity of hedonic hunger or its effect is hampered under conditions of high self-control.

Self-determination theory (SDT) lays out an imperative layout for understanding the reasons that encourage food consumption. According to SDT, two types of motivation exist: "autonomous motivation" and "controlled motivation." Autonomous motivation can be characterized by choices or decisions one makes for themselves; on the other hand, a controlled basis can be marked as the desire to satisfy others. The study reports that adults with autonomous motivation and goal setting are more likely to adapt to healthier choices like eating more fruits and vegetables. Individuals with a controlled basis are more likely to eat palatable foods, including flavorsome foods high in salt and sugar. The result was similar to other studies conducted. Some studies indicate that adolescents with higher inner drive consume a healthier diet and are resilient to hedonic hunger. Hence, they are less likely to consume too many servings of fast food. However, adults expressed opinions about how autonomous motivation develops after experiencing incidences where fast food consumption made them sick or ill. It is also to be noted that a controlled basis does not predict the consumption of palatable food. Some chances managed cause is not always associated with adverse health aspects. Findings also indicate that autonomous motivation may predict higher consumption of fatty foods and starchy foods. Dietary motivation does not fluctuate with hedonic hunger, but few studies suggest that specific clinical procedures may allow for a shift in that motivation.

The concept of self-motivation also includes a between-person trait and a within-person trait. The role of hedonic hunger as a between-person (BP) trait or within-person (WP) was examined by Cushing, 2018 which reported that between a person and within-person qualities. Demonstrated hedonic hunger. Between people trait findings included increased consumption of fatty food and within-person traits included high consumption of starchy foods, which concludes that there might be individual differences in consumption of palatable foods depending on whether hedonic hunger is between personality traits or within-person traits. Another essential predictor for hedonic hunger is a habit, and Hedonic hunger is strongly associated with practices. Unhealthy habits can reduce self–efficacy and the potential benefits of dietary planning or self-monitoring, and the desire to eat tempting foods may nullify one's routine and behavioral change. A significant positive correlation between hedonic hunger and habit was reported. The desire to eat overrules one's consciousness and one's ability to say no.

Factors affecting hedonic hunger and palatable food intake

Various environmental and external factors can have the potential to induce hedonic hunger through direct or indirect mechanisms. Studies so far have reported the correlation of multiple parameters such as obesity, motivation, self-control, abundant food environment, and the role of unhealthy dietary habits. Among all the other correlations, lifestyle habits or diet can be a significant factor influencing hedonic hunger. Some of that are listed below.

1) Emotional Eating.

Emotional eating encompasses an umbrella term influenced by certain emotional disorders symptoms such as imprudent response to a negative situation (negative urgency) or loss of interest in activities with reduced pleasure (anhedonia), which can predict an increase in hedonic hunger. Mason et al., 2020 studied

a relationship between changes in emotional disturbance problems and hedonic hunger. Since food is a coping mechanism for emotions, increased levels of hedonic hunger were seen with the increase in general anxiety, negative urgency, obsessive-compulsive disorder, and decreased anhedonia. Few studies have also shown that stress can be a recognized factor that promotes hedonic hunger or eating for reward, contributing to a larger calorie intake. Cravings for a particular type of food have also been associated with eating problems like eating disorders. There seems to be a direct relationship between food cravings and consumption of highly palatable foods, which can also lead to harmful health effects in the future, fostering the development of obesity. Food cravings usually occur for high sugar and high-fat foods and ultimately results in their consumption because of the high palatability.

2) Meals & Meal preparations

Family meals are protective and preservative for shaping an adolescent's healthy eating behaviors, reported by various Cross-sectional and longitudinal studies. The data the study conducted enumerates that feeds with the family provides an environment in which trust and communication are present, there is structured routine and ritual to occur which are likely to exhibit healthful eating behavior among adolescents In contrast adults, or adolescent who is living alone or away from home due to various reasons like for educational purposes or occupational purposes can harm health and nutritional food intake. They are more likely to choose ready-to-eat meals, including packaged foods, foods available at grocery stores and fast-food restaurants, which can negatively affect the energy intake levels by consuming more palatable foods and may play a role in developing more palatable foods hedonic hunger.

3) Social media and portion size

Non-broadcast sources of food exposure which includes social media sites like Instagram, Facebook, Twitter, etc. are likely to promote more consumption of energy-dense but nutritionally poor foods which are commonly high in sugar, fat, or salt, which can also be one of the significant risk factors for increased levels of hedonic hunger. Studies imply that different sources of food exposure and recurrent television viewing are positively linked to adolescent's intake of food and eating behavior. To a certain extent, it can be suspected that portion can also affect hedonic hunger score. Because if standard portion sizes are not followed, intake of larger portion size of high energy-dense food can act promote weight gain in children and adults

4) Sleep and physical activity

Lack of proper sleep duration and its link with a cluster of diseases like obesity, cardiovascular diseases, type 2 diabetes, and hypertension can be facilitated by dietary intake changes. According to shorter sleep duration leads to total caloric intake, fat intake, and there are limited studies for lowered intake of fruits and vegetables and a lack of quality diets. Lack of sleep or sleeping for fewer hours can also lead to irregular eating behavior, reducing the number of meals from 4-5 to fewer meals per day, and recurrent intake of calorie-dense, highly appetizing foods at night. However, the role of hedonic hunger on sleep remains unexplored, but high information on palatable foods can be considered one of the risk factors.

Concerning physical activity, it was shown that individuals with high levels of physical activity could resist consumption of high fat, non-sweet, and sweet foods and select bigger portion sizes for delayed consumption, and individuals with decreased levels of physical activity preferred consuming highly palatable foods, which was associated with increased desire and motivation for energy-dense foods. Severe session of exercise reduces the reward activity for energy-dense foods and is associated with lower desire and motivation to eat high fat, energy-dense foods

5) Other factors which influence food intake

To enlist a few of them, it mainly includes factors like eating atmosphere, which provides for odor, temperature, lighting, and noise. People consume more during winters than in summers because more energy is required to maintain their temperature. Warm or soft lighting in a restaurant can promote more consumption of foods. The effect of odor on food consumption is still unknown and not very well researched. It was shown that when the music in a cafeteria or restaurant is soft and slow, it promotes slower but higher consumption of food and drinks. Also, there is a chance of increased food intake when eaten with more people because of the relaxing and comfortable environment provided.

Extensive research in the area of factors influencing or affecting hedonic hunger is still undermined. There is a need to study and understand and a mechanism by which they induce hedonic hunger.

Conclusion

Changes in food availability both physically and psychologically have given rise to a new term called "hedonic hunger" and given rise to an eating movement that was never seen before. It is considered one of the moderating factors for obesity. The chances of being obese increase with an increase in hedonic hunger levels, and it is seen to be more prevalent in obese populations than other people with normal BMI. Eating for pleasure or enjoyment triggers a brain reward system and has shown increased response to the signals of palatable food in brain regions that underlie neural and perceptual responses. No evidence exists on the amount of food eaten during high levels of hedonic hunger, and it is only related to the individual's desire to eat palatable foods. Increasing levels of hedonic hunger can be one of the major concerns worldwide because of its adverse effects on specific diseases, dietary behavior, and overall food intake of an individual. Habits, dietary motivation, and self-control can play a role in suppressing hedonic hunger levels. Pleasure-driven hunger has caused a shift in eating patterns. While buying food, consumers focus more on the taste aspect rather than paying attention to the nutritional and health part of a particular food. The constant presence of fast foods and various delicious foods on platforms like social media and restaurants leads to widespread hedonic hunger, especially when food is just a click away. Proper nutritional and dietary interventions are required to control hedonic hunger; since food holds an integral part of our day-to-day life, it cannot be eliminated. Hence "moderation is the key." Further studies in this area should examine the role of hedonic hunger on snacking behavior, eating disorders, factors affecting it, and making food choices because these topics still lack proper evidence, especially in India.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Influence made by industrial climbing safety equipment on the cardiovascular system performance and thermophysical parameters of limbs in an industrial climber at low ambient temperatures

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Abstract

The task of the article is to assess the effect made by an industrial climbing safety system used by an industrial climber, performing his work to provide a harness-based suspended access at low ambient temperatures, on his physiological parameters. The article presents some studies on changes recorded in body surface temperatures, pulse rates, and blood pressure value in an industrial climber depending on the duration of his performance using a harness-based suspended access under ambient air low temperature conditions. The tests have been carried out for various types of thermal protection of the human hip area and the width of the belts of the safety system. The scientific novelty of the study is that it is the first time when such a study has been conducted for a combination of industrial factors, like prolonged suspended condition due to the utilization of the climbing safety system and a low ambient temperature. As a result, it has been found that the physiological parameters are influenced by the width of the safety belts of the safety equipment system and the method of the temperature protection of the hip zone in a climber.

Keywords

Influence of low ambient temperature, Blood pressure, Pulse, Industrial climber, Industrial climbing safety system

Imprint

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Introduction

The stay of a person, a climber or an industrial climber, under low ambient air temperature conditions with the mandatory use of the prescribed industrial safety system, is associated with a negative impact produced on the individual by natural hazards and industrial risk factors, as well as by some changes in the physiological parameters of the body as a result from pressing of the body with belts of the safety system [1] that negatively affects the body as a whole and the systems thereof [2,3,4].

Scientists both in Russia [5] and abroad [6] have already much studied the effect made by low ambient temperatures on the human body as a whole [7] that may cause deviations from the normal values of various organism systems to maintain the proper vital activity of the body [8]. In order to keep the thermal balance with decreasing seasonal temperatures, an individual experiences an elevated load applied to the cardiovascular system performance due to his/her physiological reactions [9,10]. It is known that the cold season is marked with a greater number of cardiovascular diseases and deaths [2,7,9], including the cases provoked due to long-term stays at low temperatures in open air [10,11]. It has been identified that the low ambient temperature exposure applied to the body increases cardiovascular loading [4], intensifies the symptoms of colds [12] and is a forerunner of a great number of heart diseases, such as hypertension [13,14,15], namely angina pectoris [16,17,18], arrhythmia [19], deep vein thrombosis [6,10,11], myocardial infarction [20,21,22], sudden cardiac death [23] etc.

When conducting a cold pressor test [24], it has been found that under the influence of low ambient temperatures, systolic and diastolic blood pressure increases in a human individual; the heart rate become greater, when performing a cold foot pressor test. Cooling of the surface tissues leads to a discomfort that may affect excitation, attention and mental concentration [25]. Cooling of the skin to low tem-

peratures causes pain, numbness and, eventually, local freezer burns [26,27].

The industrial safety system and harness permanently used by a climber may also cause harm to human health, due to the compression of the blood vessels of the legs by the straps of the safety system [28] that is manifested by numbness in the lower extremities and a discomfort in the groin area [29]. Industrial climbers, who must use in his work the industrial safety equipment systems, while suspended by their safety harness, may be at risk of rhabdomyolysis [23], loss of consciousness [30] and sudden death [31]. But in this case most often the first line of attack is the performance of the cardiovascular system that is reflected in changes in blood pressure and heart rate [27,32].

Thus, it can be seen that there are no studies available which treat a comprehensive, overall, effect on the body of a climber and an industrial climber produced by a combined action of the factors acting in parallel: both by low ambient temperatures and loading due to the mandatory use of the safety equipment system.

The aim of this study has been to assess the combined effect produced by the industrial safety system loading on the human body and low ambient temperatures affecting an industrial climber organism in parallel. We have assumed that the complex of these factors will have a negative impact on the physiological processes in the human body. We also have expected that the biggest changes would affect the body surface temperature, blood pressure and heart rate. The main data obtained were the recorded values supplied by temperature sensors, a blood pressure monitor and a pulse oximeter. Knowledge of how the industrial safety system and low ambient temperatures influence an industrial climber may be relevant to occupational health care staff involved in the study of cardiovascular diseases of climbers or industrial climbers.

Materials and methods

A man without chronic diseases has participated in our experiments as a test subject with anthropometric data as follows: height 182 cm, weight 88 kg, aged 41.

Our full-scale experiments were carried out at low ambient temperatures, utilizing various combinations of warm protective clothing and industrial safety system versions in order to determine their effect produced on the human body.

Experimental reports

A number of experiments were conducted on February 22, 2021. Before each experiment, the following data were measured and recorded: the air temperature during all experiments was within (3.3 ±4) °C; relative humidity (83.7 ± 6.5)%; wind speed (1.4 ±4) m/s. The data were properly indicated in the test report. After that, the test subject was equipped with an electronic thermometer for measuring body temperature (armpit), a wrist cuff for measuring blood pressure, a pulse oximeter for determining blood oxygen levels and heart rate (see Table 1 herein), temperature sensors placed onto different parts of the body surface; the test subject was dressed using winterized protective clothing (five different combinations).

Time limits have been defined for each experiment as given below: 20 minutes for one experiment and 30 minutes for the recovery of the test subject in a warm room to restore the normal physiological parameters.

After the temperature sensors were fixed onto the body of the test subject, he was dressed in a combination of protective clothes and a safety system specified by the experiment; then the physiological parameters of the test subject were measured and recorded; the test individual was suspended with a rope from a crossbar in such a way that he was positioned free without support for 20 minutes. The data of direct measurements delivered by the temperature sensors were displayed on the digital display of the thermometer and recorded every 2 minutes within 20 minutes for each experiment on the test report. All measurements were carried out during working hours (see Figure 1 herein).

Blood pressure

Shoulder BP was measured using automatic wrist watch (OMRON 2 Basic, China), at intervals of 10 minutes from the beginning of the tests. The arm of the subject was supported, placed onto the knee, and the cuff was positioned at the level of the heart axis.

Heart rate

Heart rate was measured using an automatic fingertip oximeter (Fingertip Pulse Oximeter, SH-01, China), at intervals of 10 minutes from the beginning of the tests. The device was applied to the thumb of the left hand of the test subject. The hand was supported, placed on the knee.

Table 1

Measured physiological data of the test subject in five experiments

The test subject wears lightweight textile trousers plus a safety system				
Time of measurement	Body temperature, °C	Blood pressure, mmHg	Pulse, beats/min	Oxygen concentration in blood, %
Beginning of the test	35	122/80	**56**	97
10 minutes after testing start	36.2	130/85	**98**	96
End of the test	36.6	130/90	**102**	95
The test subject wears lightweight textile trousers plus a safety system with downy shorts on top				
Beginning of the test	36	122/80	**95**	97
10 minutes after testing start	36.1	125/98	**96**	98
End of the test	36.3	130/90	**85**	95
The belt width of the safety system is 4.3 cm				
Beginning of the test	35.5	120/80	**91**	98
10 minutes after testing start	36.5	125/85	**93**	96
End of the test	36.8	125/90	**100**	98
The belt width of the safety system is 7 cm				
Beginning of the test	36.2	110/90	**103**	97
10 minutes after testing start	36.5	120/90	**96**	97
End of the test	36.7	120/90	**95**	97
The test subject wearing warm down trousers, equipped with a safety system with a strap width of 4.3 cm as well as lightweight cotton shorts worn over				
Beginning of the test	35.5	110/90	**95**	96
10 minutes after testing start	36.2	120/90	**106**	97
End of the test	36.7	120/90	**108**	96

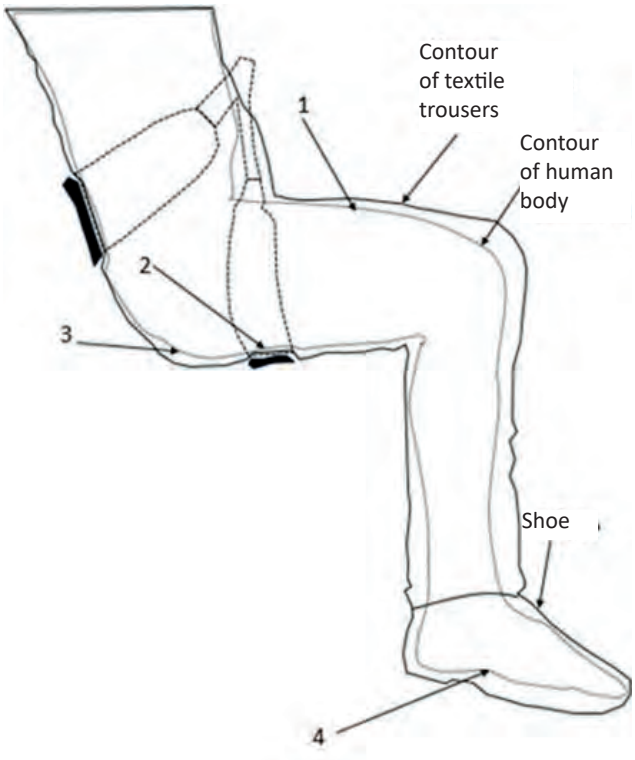

Figure 1. Points of locations of temperature sensors: sensor No. 1 (on the surface of the hip), sensor No. 2 (on the body surface under the safety system belt), sensor No. 3 on the body surface in the buttock area, sensor No. 4 (on the foot surface) in shoes

Digital data of temperature sensors (skin surface temperature)

The skin temperature was measured by sensors placed at certain points of the skin surface, every 2 minutes for the period of 20 minutes of each test using a small-sized digital thermometer (TCM 1520 (incorporated five remote sensors), Russia), and the data were indicated in the test report.

The sensors were placed as follows: sensor No. 1 on the upper surface of the hip, below the hip strap of the safety system; sensor No. 2 under the strap of the safety system, on the hip; sensor No. 3 on the body surface of the test subject, in the buttock area, above the hip strap of the safety system; sensor No. 4 was placed on the foot surface of the test subject). Heat losses were estimated by the arithmetic mean of 10 measurements for each sensor.

Results

Thermoregulatory reactions

Based on the results of five experiments in various protective clothing configurations and the safety systems with different strap thicknesses, summary diagrams for each temperature sensor have been constructed as given in Figure 2 A, B, C, D herein.

The effect produced by low ambient temperatures on a human individual in all experiments with various combinations of winterized protective clothing has shown, in general, the dynamics of a decrease in the body surface temperature values recorded by all sensors. Thus, sensor No. 1 in the hip area in front has recorded a decrease of 3°C in the skin surface temperature in all experiments; sensor No. 2, fixed under the strap of the safety system on the body surface, has recorded a decrease in the skin surface temperature by 2.2 °C; sensor No. 3, applied to the skin surface in the buttock area, has delivered the measurements decreased by 2.7 ° C, and sensor No. 4, fixed on the foot skin surface, has documented a decrease by 2 °C, respectively. According to the individual feelings of the test subject, numbness of the legs has appeared upon completing half of testing (10 minutes after test starting), and it has been reported that the lower part of the body has begun to freeze after a third of the experiment time (5-6 minutes before the end of the experiment) reaching the state "very cold".

Blood pressure and heart rate

The effect produced by low ambient temperatures on a human individual, working with the use of industrial climbing safety equipment with a harness-based suspended access has demonstrated that during all the experiments the recorded body temperature has been found to be stable. The exposure to low ambient temperatures has resulted in an increase in the systolic blood pressure by an average of 8 mmHg and in the diastolic pressure value by 5 mmHg. The reported heart rate values in the different experiment configurations (sets of protective clothing used) show highly variable results. For example, when tested in lightweight textile protective trousers with the use of an industrial climbing safety system, the number of heart beats per minute has increased more than 2 times (from 56 to 102 beats/min.). Most likely, this is due to heavy physical load experienced by an individual when working with the use of industrial climbing safety equipment with a harness-based suspended access that is a sort of stress for an untrained organism. It is an important indicator that the cardiac system is under heavy loading, and a rise in the pulse over 100 beats per minute is classified as tachycardia, that is a marker of the incapability of the heart to efficiently deliver blood in the organism. Of course, this unfavorable condition is neutralized as soon as the person returns to his usual environment, and it does not cause serious complications and or a discomfort. But if this load is applied to the human body on a regular basis, then the risk of developing a heart disease becomes greater. So taking into account the individual characteristics of each person, the above indicator may serve as a transitional case towards developing an occupational disease. When wearing warm down shorts in addition to the above set of protective clothing, the difference in the heart rate before the test and after it has been found to be minimized and has become even smaller (from 95 to 85 beats/min) that is probably due to an additional heat insulation of the affected area and a more comfortable condition for the test subject.

Discussion

Our experimental study is the first research designed to assess the physiological parameters of a human body of an individual working with the use of industrial climbing safety equipment with a harness-based suspended access under exposure to low ambient temperatures and other unfavorable atmospheric factors, similar to usual everyday working

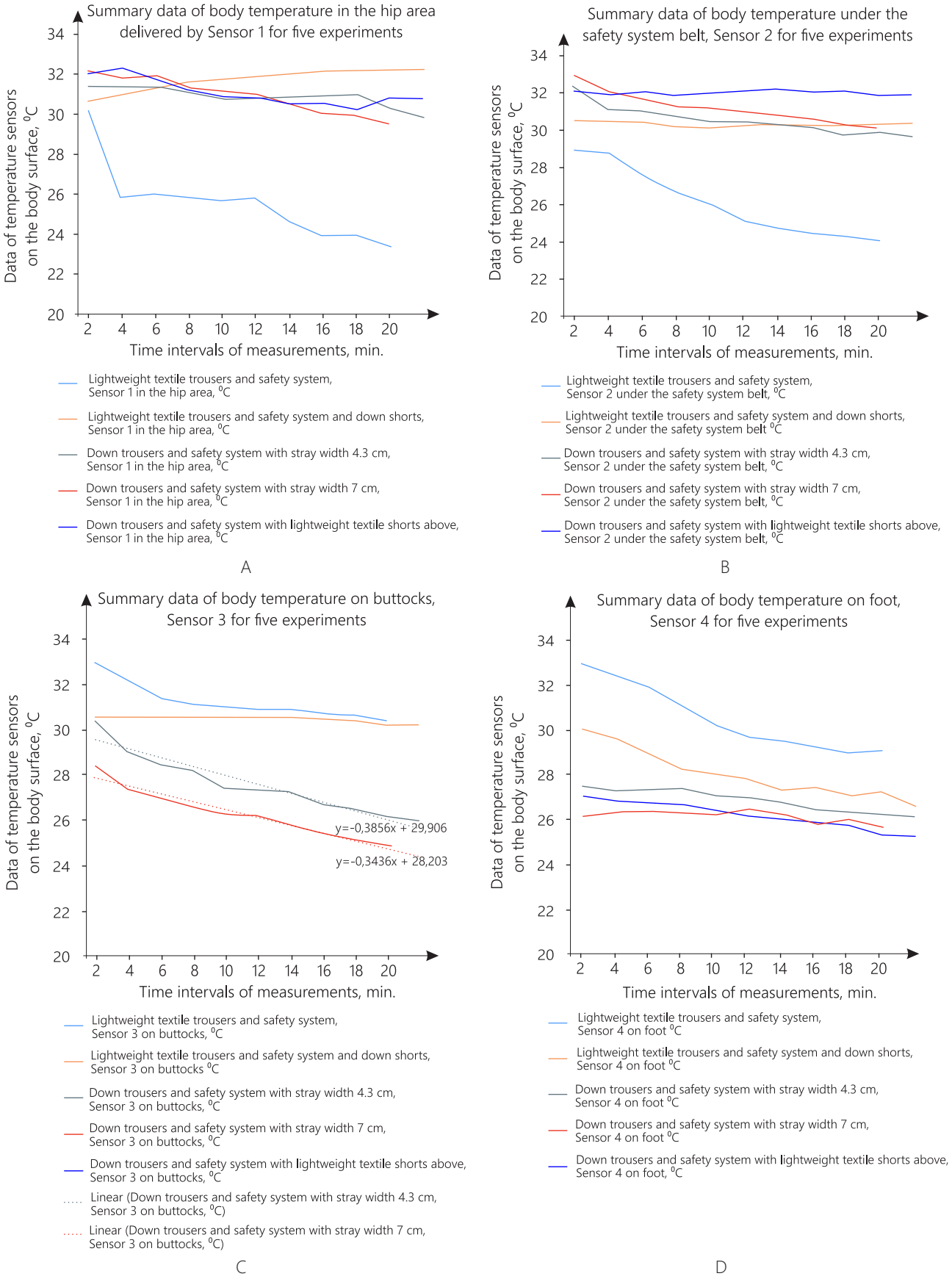

Figure 2. Summary diagrams of body temperature data delivered by sensors No. 1, 2, 3, 4 for five experiments

conditions. Although the effect made by low ambient temperatures has not been found significant , we have observed that it has resulted in lowering the body surface temperature in the test subject according to the evidence data delivered by all temperature sensors in all sets of our experiments covering all sets of protective clothing that as a consequence may negatively affect the performance of an industrial climber under working conditions and reduce the total time required for the work completion; with regular heat loss when undertaking the regular occupational activity, it may provoke the onset of diseases, with the potential to convert the disease to an occupational one.

According to our results, a short-term exposure to low ambient temperatures (20 minutes) leads to an increase in blood pressure, however not to critical values thereof, that does not affect the overall performance of a person. The observed increase and decrease in the heart rate, depending on the set of protective clothing, may indicate possible frequent problems of the cardiovascular system performance with respect to tachycardia and arrhythmia.

Previous experimental and clinical trials studying the effect produced by low ambient temperatures on the human body [2], including the performance of the cardiovascular system [33] and other systems in the human organism [9,16,14, etc.] were carried out without loading applied to the test subject body due to the use of industrial climbing safety equipment with a harness-based suspended access. Also, some tests conducted with rope-based suspended access [23] did not take into account the effect made by low ambient temperatures on the body of a working person: they were mostly aimed at studying of the industrial climber performance, who used not the industrial climbing safety system, but who employed the rope suspension systems only [32,30].

Conclusions

As a result of the presented sets of tests, it has been found that the systolic and diastolic blood pressure in the test subject has increased by an average of 10 mmHg in all experiments for different protective clothing configurations. At the same time, the heart rate values have demonstrated their instability. Probably, with an increase in blood pressure, the heart rate should also be greater. A detailed analysis has revealed that the complete set of the winterized protective clothing may influence the heart rate values. The fact is that when a climber applies his industrial climbing safety system onto his trousers, including the winterized version thereof, his protective clothing is pressed by the straps of the safety system, so that some "body heat loss points" appear, which may provoke intensive heat losses, and the climber experiences general discomfort, stress and shows some other changes in his physiological body parameters (the heart rate increase from 56 to 102 beats/min for 20 minutes of the experiment). But when later the same test subject has been experienced some more comfortable conditions, using warm downy shorts over the set of his protecting clothing, we have observed the body's response: the heart rate reduction (from 95 to 85 beats/min for 20 minutes of the experiment). This is probably due to the fact that the test subject has recovered his comfortable warm state, relaxed, and the stress loading applied to the body has been minimized. The same response has been observed with the use of different versions of the industrial climbing safety systems. When in the first experiment we have utilized a system configuration with a strap width of 4.3 cm for the test subject, the heart rate has increased (from 91 to 100 beats/min for 20 minutes of the experiment). But as soon as in the second experiment we have applied another safety system with straps 7 cm wide, the body has "calmed down", the test subject has experienced more comfort working with the harness-based suspended access; stress has been eliminated, and the pressure on hips has been minimized; the heart rate has decreased (from 103 to 95 beats /min for 20 minutes of the experiment). By this means it can be concluded that the physiological parameters of the human body exposed to low ambient temperatures depend on the degree of additional thermal protection of the hip area and on the width of the straps of the industrial climbing safety system used by a working person.

The obtained results are the basis for the development of some fresh design concepts for protective clothing and industrial climbing safety systems to improve the working conditions and reduce the physiological load experienced by an industrial climber.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Clinical and laboratory indicators of patients with type 2 diabetes mellitus on the background of freeze-dried camel milk «shubat extra» medication

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Abstract

Camel milk is a natural product that has dietic and medicinal properties. Camel milk is widely used in the field of non-conventional medicine. It is scientifically proven that camel milk has the ability to help in the medical treatment of cancer and leukemia, due to the presence of substances that eliminate out of the body the compounds that provoke the development of cancer. In addition, such milk is used during the treatment of tuberculosis, ulcers and some other problems with the gastrointestinal tract. This product is recommended to use for problems with the pancreas, liver and intestines, as well as diabetes mellitus.

The goal of research was to study the clinical parameters of patients with type 2 diabetes mellitus. The study group consisted of 15 patients with medium severity. The patients took freeze-dried shubat (camel milk) for 60 days. As a result of the treatment, an improvement in clinical symptomatology and laboratory parameters was achieved in all patients with diabetes mellitus. The results of the study showed the therapeutic and dietary potential of camel milk, due to its unique quality composition.

Keywords

Camel milk, Shubat, Diabetes mellitus, Nutrition

Imprint

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Introduction

Since ancient times, camel milk has been valued not only for its nutritional value, but also for its medicinal properties. Many authors have studied microbiota of national lactic acid products, including shubat [1-9]. Also, scientists have found that camel milk helps to stabilize diabetes mellitus, because it has a high concentration of insulin. The therapeutic value of camel milk in the treatment of stomach ulcers and hepatitis was studied by Academician T.Sh. Sharmanov. and employees [1]. Also, scientists [2] conducted successful treatment of chronic intestinal enteritis and dysbacteriosis using camel milk.

Camel milk is considered a rich source of protein – it contains lysozyme, lactoferrin, lactoperoxidase, immunoglobulins, as well as a protein that determines peptidoglycans, which was found only in camel milk [3]. It was also found that camel milk contains a low amount of β-casein and no β-lactoglobulin, so it can be consumed by people suffering from cow's milk allergy [1-4]. The lactose of camel milk, in comparison with cow's milk, is easily metabolized; therefore, it can be recommended for persons with lactose intolerance [4].

The content of vitamin C in camel milk is three times higher than in cow's milk and one and a half times higher than in mother's milk. In the studies of the authors, a high content of such minerals as sodium, potassium, ferrum, cuprum, zinc, selenium and magnesium was found in camel milk [5]. According to the results obtained by Abdel-Hameid, who studied the nutritional value of camel milk, the average protein content was 4.02 ± 0.1% and varied from 3 ± 0.3% to 4.5 ± 0.2%. The main carbohydrate in milk is milk sugar – lactose, its amount in camel milk was 3.8 ± 0.1% and ranged from 3.3 ± 0.2% to 4.7 ± 0.3%. The moisture content in camel milk varied from 87.5 ± 0.8% to

91.6 ± 0.6% with an average value of 89.5 ± 0.4%. The average fat content in camel milk was 2.8 ± 0.2% with changes in the range from 2 ± 0.1% to 3.4 ± 0.3% [6].

There is some information about the positive effect of camel milk and shubat in diabetes mellitus, that treatment with chal leads to the normalization of the intracellular function of the pancreas, and the number of patients with a normal type of glycemic curves increases. In Kazakhstan, the cases of a blood sugar confident decrease were observed in patients who used shubat at home. This question is very important and interesting: the number of patients with diabetes mellitus in the world is increasing every year. It is necessary to comprehensively study in a clinical setting the effect of camel milk and shubat on patients with diabetes mellitus.

Diabetes mellitus is in third place in the list of death causes after cardiovascular and oncological diseases. This disease affects about 1 million people all over the world. It is common practice for diabetics in Africa, Asia and the Middle East to self-medicate with camel milk. Studies have shown that camel milk contains a high concentration of insulin – 150 U / ml, although insulin is present in human, cow and goat milk, it is broken down in the acidic environment of the stomach. This does not happen with camel milk, which does not react to acid and in this case no coagulate is formed.

The use of camel milk for ulcers, if we take into consideration the fact that the generally accepted cause of ulcers is a bacterium, then the bactericidal properties of camel milk will be effective. Complete healing of ulcers in 57.5% of patients after consuming camel milk is described in the works of a number of researchers. The peptidoglycan-identifying protein has an affinity with heparin, that allows us to conclude about its role for blood vessel development (wound healing), this is essential for the treatment of gastric and duodenal ulcers.

The synergistic effects of peptidoglycan-identifying protein, lactoperoxidase and lactoferrin inhibit the growth of gram-negative bacteria, such as Helicobacter pylori, which cause ulcers. Lactoperoxidase remains resistant to pH acidity and protein breakdown and is therefore active in both the stomach and intestines. The connecting link is that the reason for the use of camel milk in the stomach cancer treatment was the fact that after the stomach ulcers treatment with antibiotics, remission of stomach cancer occurs [7].

There is no β-lactoglobulin and new β-casein in camel milk which allows children suffering from allergies in the absence of β-globulin associated with milk protein to drink this milk.

After bacterial infection, rotavirus infection is the most dangerous factor in causing diarrhea in young children. Camel milk has antibacterial and antiviral properties and works against bacteria in the gastrointestinal tract. Lactoferrin saturated with ferrum (from the second week of lactation) prevents the growth of microbes in the intestines; Camel peptidoglycan-identifying protein may inhibit the growth of gram-positive bacteria, such as bacilli strains; lactic acid bacteria (lactobacilli, lactococci, streptococci, etc.), which cause diarrhea.

Lactoferrin contained in camel milk, is used to treat respiratory problems. Laboratory studies have shown that camel milk contains a lot of prostaglandins, one of the remedies for the treatment of respiratory diseases [4-9].

The literature review shows that proteins in camel milk have not been fully investigated. In Kazakhstan, the company "BB Partners" LLP produces a freeze-dried form of camel milk in the form of a powder using modern innovative technology by evaporation at a low temperature (down to -50 ° C) with appropriate pasteurization. This technology contributes to the preservation of biologically valuable components of the product, and also increases the shelf life.

The goal of research: determination of the chemical composition of freeze-dried camel milk powder, study of clinical and laboratory parameters of patients with diabetes mellitus of mild and moderate severity in connection with the use of "Shubat Extra".

Materials and methods

The component composition of camel milk powder, physical and chemical characteristics, the content of lipids, amino acids, vitamins and minerals were studied by chromatographic methods of analysis.

Powdered camel milk by organoleptic characteristics is a homogeneous white powder, taste and smell are clean, characteristic of fresh pasteurized milk, the consistency of milk is a fine dry powder. The nutritional value of the product per 100 g of milk powder is: proteins - 4.08 g, fats - 5.64 g, lactose - 4.72 g, antioxidants - 52.32 g (Table 1).

As it is known, the biological and nutritional value of a food product is determined by its amino acid

Table 1

Physical-chemical indicators of freeze-dried camel milk powder "Shubat Extra"

Name of indicators, units of measurement	Actual results	Reference documentation for test methods
1	3	4
Physical and chemical indicators:		
- mass fraction of protein,%	4,08±0,06	GOST 34454-2018
- mass fraction of fat,%	5,64±0,05	GOST ISO 1736-2014
- content of antioxidants, mg / 10g	52,32±0,2	GOST P 54037-210
- mass fraction of lactose,%	4,72±0,2	GOST 34304-2017
Vitamins, mg / 100g		
- A	0,037±0,0007	GOST P 54635-2011
- C	7,84±0,1	GOST 34151-2017
- E	0,12±0,002	GOST EN 12822-2014
Mineral elements		
- Calcium	119,81±2,99	GOST ISO 12081-2013
- Magnesium	25,1±0,37	GOST ISO8070/IDF119-2014
- ferrum	0,09±0,002	GOST ISO/TS 6733-2015
- cuprum	14,61±0,21	GOST ISO/TS 6733-2015
- zinc	0,37±0,007	GOST ISO/TS 6733-2015
- phosphorus	92,03±1,84	GOST P 51482-99
- sodium	66,1±1,32	GOST ISO 80701/IDF119-2014
- potassium	181,4±3,62	GOST ISO 80701/IDF119-2014

composition, primarily the content of essential amino acids. The amino acid composition of freeze-dried camel milk powder is given below, the amino acids arginine 72.0 mg/l, leucine + isoleucine 10.0 mg/l, and proline 21.0 mg/l prevail in it. It contains all the essential amino acids (Table 2).

Table 2

Amino acid composition of freeze-dried camel milk (shubat) powder according to M-04-38-2009

No.	Component	Concentration mg / l	Mass fraction of amino acids
1	Arginine	72.0	1,78±0,72
2	Lysine	8.60	0,21±0,07
3	Tyrosine	7.50	0,19±0,06
4	Phenylalanine	6.10	0,17±0,06
5	histidine	5.50	0,14±0,07
6	Leucine + Isoleucine	10.0	0,25±0,07
7	methionine	4.50	0,11±0,04
8	valine	7.00	0,18±0,07
9	proline	21.0	0,51±0,14
10	threonine	7.30	0,18±0,07
11	serine	8.40	0,21±0,06
12	alanine	4.10	0,10±0,03
13	glycine	1.90	0,05±0,02

Studies on the lipid composition of milk powder were carried out by the method of gas chromatographic determination of fatty acids and cholesterol in food products M-04-38-2009. The results of the performed studies indicate that the content of fatty acids in mare's milk powder was found in the amount of 27 (Table 3).

Table 3

Fatty acid composition of freeze-dried camel milk (shubat) powder according to GOST 30623-98

No.	Component	Concentration,%
1	Methyl Butyrate	2.10
2	Methyl hexanoate	83.254
3	Methyl decanoate	0.054
4	Methyl undecanoate	0.0336
5	Methyl Laurate	0.0653
6	Methyl Tridecanoate	0.0107
7	Myristoleic acid methyl	0.1588
8	Methyl Myristate	0.054
9	Cis-10-Pentadecenoic acid methyl ester	1.9115
10	Methyl Pentadecanoate	0.1453
11	Methyl Palmitoleate	0.3316
12	Methyl Palmitate	0.4521
13	Cis -10-Heptadecenoic acid methyl ester	2.5458
14	Methyl Heptadecanoate	2.3258
15	Gamma Linolenic acid methyl	0.3102
16	Methyl Linolenate	0.1081
17	Linolelaidic acid methyl ester	1.4193
18	Cis-9-Oleic acid methyl	4.0838
19	Trans -9- Elaidic acid methyl ester	0.3342
20	Methyl Stearate	0.1262

21	Methyl cis -5.8.11.14.17 -Eicosapentaenoate	0.00453
22	Methyl cis -5.8.11.14- Eicosatetraenoic	0.0865
23	Cis -11.14.17 –Eicosatrienoic acid methyl ester	0.0041
24	Cis -8.11.14 –Eicosatrienoic acid methyl ester	0.0164
25	Cis -11.14 –Eicosadienoic acid methyl ester	0.00503
26	Methyl cis -11 Eicosenoate	0.0091
27	Methyl Heneicosanoate	0.01176
		Σ 99,99

The study group consisted of 15 patients with type 2 diabetes mellitus, among them 3 men and 12 women received «Shubat Extra» therapy, which was used as an additional therapy. All subjects took 1 capsule 3 times a day, and a set of generally accepted studies was carried out. It included an analysis of the peripheral blood morphology, laboratory studies of urine. **Glycated hemoglobin (HbAc1) test**. The effect of "Shubat Extra" on sugar level was measured by measuring the blood in the fasted state, testing blood sugar level (2 HPG) and glycosylated hemoglobin (HbA1c) 2 hours after a meal, above 6.5% indicated the presence of type II diabetes mellitus. Serum C-peptide and change in body weight were also evaluated.

Also, in addition to taking «Shubat Extra » , patients were recommended 2 months of diet therapy, physical activity depending on age. As a result of taking "Shubat Extra", the patients' condition improved. Such complaints as thirst, weakness, drowsiness disappeared. The appetite decreased in everyone. A decrease in weight was noted in all patients, which accordingly improved the quality of life. In dynamics, during the control study of blood glucose indicators, its decrease was noted. Table 4 shows the data of blood glucose analyzes before and after taking "Shubat Extra".

Table 4

Dynamics of laboratory indicators in patients with diabetes mellitus with moderate severity

Number of patients	Age	Men	Women	Blood glucose content	
				Before	After 2 months
15	45-65	3	12	7-10 mmol/l	5.8-7.0 mmol/l

Results of the study and their discussion

According to the analysis of the physical-chemical composition of freeze-dried camel milk (shubat) powder, the energy value per 100 g of the finished product: 86.50 kcal / 362 kJ, nutritional value per 100 g of the finished product: proteins –4.11 g, carbohydrates -5.45 g, fats -5.53 g. An important carbohydrate of milk is milk sugar – lactose, its amount in camel milk was 4,72 ± 0.2%. The results of the study showed an improvement in clinical symptoms in all patients. Blood glucose in the fasted state decreased at 2, 4 and 6 weeks. HbAlc decreased by 1.42% by the end of 8 weeks of treatment.

The use of «Shubat Extra» at a dose of 1.2 g / day also showed an improvement in all measured parameters. However, no increase in the usefulness of a dose of 2.4 g per day, 3.6 g per day of milk was observed. The results of this study show that a dose of 2.4 g of milk per day is recommended to be additionally applied to hypoglycemic agents for type 2 diabetics.

Conclusions

This research has shown the effectiveness of the use of freeze-dried camel milk (shubat) powder "Shubat Extra" in type 2 diabetes mellitus, which is associated with its unique qualitative composition. Due to the natural progression of type 2 diabetes mellitus, in order to maintain good glycemic control, it is necessary to take «Shubat Extra» in combination with general therapy, diet therapy and physical activity, which makes it possible to recommend its use for diabetes mellitus.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Chemical composition and nutritional value of the fish grown under the conditions of a natural hot spring of the Almaty region

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Abstract

The article presents the results of the study of the nutritional, biological value and the chemical composition of the Nile tilapia fish, grown in the natural hot spring of Chondzhy, using different formulations of grower feed. Also, the chemical composition and nutritional value of the sharptooth catfish were investigated for comparative analysis. Nutritional value was characterized by the content of water, nitrogenous matter, lipids, minerals, carbohydrates and vitamins. It was found that this feed additive is completely harmless, does not have negative consequences.

Keywords

Health effects, Fish, Feed additives, Chemical composition, Nutritional value, Safety

Imprint

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Introduction

Tilapia is a huge number of fish species belonging to different genera of the same cichlids family, fish have valuable biological and economic qualities. In the 70s of the XX century, the genus of tilapia included a little more than 100 species, the distribution zone was mostly tropical regions of the world (Central America, Africa, Southeast Asia and the Middle East) [1]. Tilapia have ease of reproduction, rapid growth, high viability, wide ecological plasticity, tilapia with the excellent nutritional qualities are of undoubted interest for aquaculture in Kazakhstan [2].

In terms of the production growth rate, one of the first places is occupied by tilapia. If in 1974 the world production of tilapia was about 300 thousand tons, then in 1990 it reached 800 thousand tons, and in 2005 it was double more and exceeded 1.6 million tons [3].

Such a rapid spread of tilapia in the world aquaculture and a significant increase in its production is explained by a number of valuable biological features and economically useful qualities that are inherent in these fish.

It should be noted that tilapia are not only a prospective object of aquaculture, but also an excellent model for experimental research due to a number of biological features.

The size, chemical composition and nutritional value of fish depend on its species, age, gender, physiological state and living environment. Experts agree that, even in small amounts, fish can have a significant positive impact on improvement of dietary protein quality by supplementing the essential amino acids, which are often found in small amounts at the heart of a plant-based diet. But recent research shows that fish is much more than just an alternative source of animal protein. Tran oil is the richest source of a type of fat that is vital for normal brain development in newborn babies and infants. Without sufficient amounts of these fatty acids, normal development of the brain does not occur [4].

Fish *proteins* (5-25% and more) make up about 85% of the nitrogenous substances amount and are not inferior in terms of biological value to homoithermic animals meat proteins. Fish proteins are complete, and are mainly represented by simple proteins, which are subdivided into *water-soluble proteins* (myoglobin, globulin-X, myoalbumin); *salt-soluble* (meosin, actin, actomeosin, tropomeosin); *complex proteins* insoluble in water and salt solutions, but soluble in alkalis and acids: nucleoproteins, phosphoproteins, glucoproteins [5].

Proteins that make up muscle tissue are found mainly in a colloidal state in the form of gels and sols. This predetermines the instability and variability of the properties of protein substances [6].

According to *AboutOrganics*, only fish grown in special farms can be labeled as «organic».

The goal of research is to study the nutritional and biological value, the chemical composition of the Nile tilapia fish, grown in the natural hot spring of Chondzhy, using different formulations of grower feed. Also, the chemical composition and nutritional value of the sharptooth catfish were investigated for comparative analysis.

Materials and methods

Experimental studies were carried out in the conditions of a natural hot spring in the Almaty region. 4 groups of Tilapia and 4 groups of sharptooth catfish were formed for this aim in different age groups, which were kept in specialized rectangular pools without attachment. The optimal water temperature for Tilapia was 20-26 ° C, for catfish it was 15-18 ° C, the optimal concentration of oxygen dissolved in water for Tilapia was 20-21 ° C, the optimal concentration of oxygen dissolved in water for catfish was 9-12 mg/l. (МАРК-302Э - dissolved oxygen analyzer).

Sampling and organoleptic studies were carried out in accordance with the temporary methodology guidelines "Veterinary and sanitary examination of products of animal origin", ST RK 1802-2008 Fish, seafood and products of their processing. Rules for acceptance and sampling, GOST 7631-85 "Fish, marine mammals, marine invertebrates and products of their processing. Acceptance rules, organoleptic quality assessment methods, laboratory test sampling methods ", ST RK 1803-2008 Fish and seafood. Sensory assessment methods. The fish were gutted, packed in ice and taken to the laboratory on the day of slaughter, all analyzes were performed the next day.

The chemical composition of fish flesh was determined by a set of methods: moisture - by drying at 105^{0}C, tran oil - according to Soxhlet, total protein - by the modified Kjeldahl method, minerals - by burning in a muffle furnace (AOAC, 1980). Ash was determined using a muffle furnace with heating at 550° C for 8 hours. The calorie content of flesh was determined according to the Aleksandrov formula.

All data were subjected to one-way analysis of variance (ANOVA) using the Statistica 8.0 software to test the effects of experimental diets. All results are expressed as mean values ± SD.

Research results

The chemical composition of fish flesh, which determines its nutritional value and tastiness, is characterized, first of all, by the content of water, nitrogenous matter, lipids, minerals, carbohydrates and vitamins. The chemical composition of fish is not constant. It depends significantly on the species, physiological state, age, gender, habitats and other factors.

Table 1 provides the results of proteins, fats and ash concentration in the muscle tissue of Tilapia. In our experiments, with a comparative assessment of the flesh quality, it was found that the protein content in the flesh of tilapia from the group 3 was higher comparing with the other groups. The amount of protein in flesh was 15.71 ± 0.32 g / 100g in the first group, 16.86 ± 0.28 g / 100g in the second experimental group, – 17.72 ± 0.37 g / 100g in the third, 16.07 ± 0.55 g / 100 g in the fourth experimental group, respectively.

The results of the studies carried out indicate a high protein content in the flesh of the fish fed with feed based on the compound grower feed, which allows us to conclude about the high nutritional value

Table 1

Chemical composition and nutritional value of tilapia flesh from experimental groups when using the grower feed formulation

Indicators, Measurement units	Experimental groups of tilapia (n = 20)			
	1	2	3	4
	tilapia (grown in ponds)	tilapia (juveniles and spawners)	tilapia (optimal starting)	tilapia (grown in pools)
Protein, g / 100g	15,71±0,32	16,86±0,28	17,72±0,37	16,07±0,55
Tran oil, g / 100g	5,44±0,14	5,91±0,13	6,42±0,21	5,35±0,12
Moisture, g / 100g	74,97±1,23	73,45±1,65	73,08±1,37	73,99±1,14
Ash, g / 100g	1,04±0,87	1,28±0,52	1,45±0,41	1,14±0,24
Energy value kcal / 100g	115,60±3,67	114,45±3,62	115,28±4,25	113,35±4,14

and these feed recipes application perspectiveness in the production of high-quality fish products.

The moisture content in the experimental group of fish was normal. A slight increase in the moisture content was observed in the flesh of the first experimental group, which increased by 2.02% in comparison with the second group, the third experimental group - by 2.52%, and the fourth - 1.3%. The conducted studies on the moisture content indicate that the grower feed formulation does not have a negative effect on the moisture content of the meat (Figure 1).

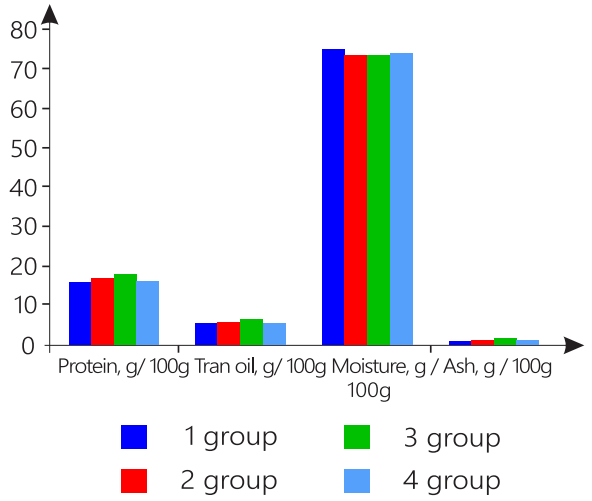

Figure 1. The chemical composition and nutritional value of tilapia flesh in the experimental groups when using the compound grower feed formulation (g / 100g)

The tran oil content was 5.44 ± 0.14 g / 100g in the fish flesh of the first group, 5.91 ± 0.13 g / 100g in the second, 6.42 ± 0.21 g / 100g in the third, 5.35 ± 0.12 g / 100g in the fourth.

The ash content in all groups is practically at the same level (from 1.04 g / 100g to 1.45 g / 100g). The current values obtained from the study are almost the same with the results of the study of various salmon species published in Testi's reports [7].

The energetic value of the tilapia flesh when using the compound grower feed formulation increased in the experimental groups of tilapia of group 1 (grown in ponds) and 3 (optimal starting), apparently, this is due to the fact that at such recipe concentrations, this compound grower feed is better taken up by fish.

Table 2 shows the chemical composition and nutritional value of the flesh in the experimental groups of sharptooth catfish when using a new compound feed formula in the diet. According to the research results, it was found that the protein content significantly increased in the experimental group 2, where the sharptooth catfish weighing from 3 to 25 grams were studied, compared to the experimental group 4. For example, the amount of protein was 16.71 g / 100g in the flesh samples of the 4th experimental group (weight from 100 to 500 grams), then it significantly increased in the first and second experimental groups to 4.62% and 7.57%, respectively. And the amount of protein in the third group was 17.09 g / 100g. Thus, there was an increase in the amount of tran oil in the third experimental group in comparison with the rest of the groups. The amount of tran oil was 7.28 g / 100g in group 3, while it noticeably decreases to 0.42 and 0.80 g / 100g in the first and second groups. And, the amount of tran oil in the 4th experimental group of catfish is 7.19 g / 100g (Figure 2).

Table 2

Chemical composition and nutritional value of the sharptooth catfish flesh in the experimental groups when using the compound grower feed formulation

Indicators Measure units	**Experimental groups (n = 50)**			
	1	**2**	**3**	**4**
	Sharptooth catfish juveniles weighing from 25 to 50 grams	**Sharptooth catfish underyearlings weighing from 3 to 25 grams**	**Sharptooth catfish weighing from 50 to 100 grams**	**Sharptooth catfish weighing from 100 to 500 grams and above**
Protein, g / 100g	17,55±0,22	18,08±0,47	17,09±0,43	16,71±0,12
Tran oil, g / 100g	6,86±0,33	6,48±0,51	7,28±0,12	7,19±0,08
Moisture, g / 100g	77,72±1,55	77,02±1,24	77,89±1,37	78,67±1,41
Ash, g / 100g	1,61±0,24	1,65±0,43	1,56±0,47	1,47±0,79
Energy value kcal / 100g	90,45±3,54	90,97±3,22	88,35±3,19	89,60±2,90

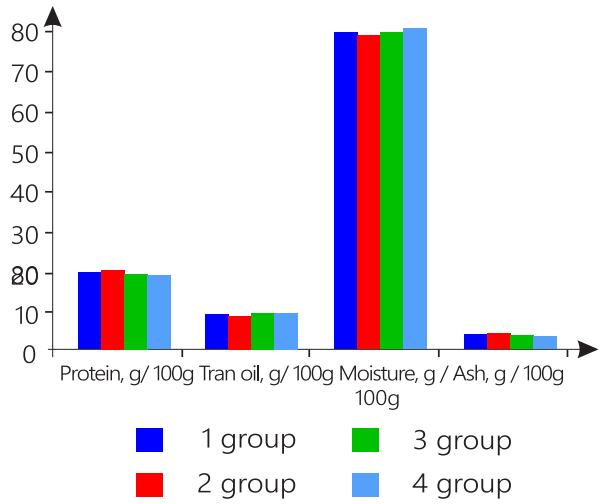

Figure 2. Chemical composition and nutritional value of the sharptooth catfish flesh in the experimental groups when using the compound grower feed formulation (g / 100g)

The moisture and ash content in the experimental groups remained practically unchanged. If the moisture content reached 77.72 g / 100g in the first group, then it was 77.02 g / 100g in the second, 77.89 g / 100g in the third, 78.67 g / 100g in the fourth, respectively. The ash content also remained unchanged, all indicators were normal. Its amount was 1.67 g / 100g in the first group, 1.65 g / 100g in the second experimental group, 1.56 g / 100g in the third, 1.47 g / 100g in the fourth.

The results of the sterlet sturgeon flesh study show that the use of the Zeofish feed additive in the fish diet does not negatively affect the chemical composition of the flesh. The assimilation of the feed additive by sterlet sturgeon also remained within the normal range, as in the experimental groups of rainbow trout.

The results of the energy value analysis showed an increase in this indicator in the fish of the first, third and fourth experimental groups. The implication is that the more Zeofish feed additive in the diet, the better the condition of the fish organism, the energy value increases in proportion to the content of Zeofish feed additive in feed.

Thus, as a result of the chemical composition and nutritional value study of valuable fish species flesh (rainbow trout and sterlet) in the food consumption if which an unconventional feed additive Zeofish was supplemented, it was found that this feed additive is completely harmless, does not have negative consequences on the chemical composition of the experimental groups fish flesh, while there was a noticeable increase in some indicators in the experimental groups: protein in the first experimental group by 0.81%, in the second experimental group by 1.25%, in the third by 1.93%, in the fourth experimental group by 3, 16%, tran oil by 0.37%, 0.18%, 0.55, 0.74%, respectively.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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ORIGINAL RESEARCH

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Comparison of coronary vessel sizing using coronary angiography versus intravascular ultrasound in Egyptian patients

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Abstract

Background: Coronary artery disease (CAD) is a leading cause of death worldwide. Intravascular imaging is an important tool in the arsenal of each interventional cardiologist. While angiography provides a two-dimensional image of a three-dimensional structure, intravascular imaging enhances understanding by providing detailed cross-sectional images. This study aimed to investigate the discrepancies in coronary vessel sizing between quantitative coronary angiography (QCA) and intravascular ultrasound. Methods: This cohort study was conducted on 69 patients who were referred for elective coronary angiography. Patients were subjected to history taking, examination, blood samples, electrocardiogram (E.C.G.), and echocardiography. Then, a comparison of each vessel's luminal diameter by QCA and IVUS was done. Results: The study included 69 patients; The mean age was 54.7 ± 9.7. There was a statistically significant difference between the studied vessels regarding the discrepancy between luminal diameters measured by IVUS and QCA. IVUS luminal diameter was larger than QCA luminal diameter (the median difference in measures of QCA and IVUS in the left main artery, LAD, LCX, and RCA were -0.8, -0.55, -0.4, and -0.5 respectively). Furthermore, there is a statistically significant difference between the studied vessels regarding the presence of a difference >0.75 mm between the luminal diameters measured by IVUS and QCA (Difference >0.75 mm in the left main artery, LAD, left circumflex and RCA were 55.8%, 21.7%, 30.8%, and 15.4% respectively). Conclusion: Coronary lesions were underestimated by QCA in comparison to IVUS regarding luminal diameter, especially the left main (LM).

Keywords

IVUS, QCA, Vessel sizing

Imprint

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Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide [1]. Coronary revascularization is the most important strategy for coronary artery disease [2]. Quantitative coronary angiography (QCA) has played a crucial role in evaluating interventional techniques [3]. Meanwhile, QCA is subjected to the limitations of two -dimensional imaging, such that it can underestimate disease severity, particularly when positive remodeling has occurred [4]. Recently, intravascular ultrasound (IVUS) is a useful tool during the PCI procedure for providing information on preintervention lesion characteristics, including vulnerable plaques, lesion severity, length, and morphology; on postintervention optimal stent implantation for stent expansion, extension, and apposition; and on possible complications after stent implantation [5]. Mis-sizing of the stent promotes intimal hyperplasia (IH) due to the impact of endothelial shear and intramural stress. Thus, optimal stenting requires correct sizing of the stents, as both oversizing and under-sizing are highly inducive to IH and that predisposes to thrombosis [6]. The use of IVUS guidance in PCI is associated with lower long-term mortality, MI, and repeat revascularization [7].

The objective of this study was to study the discrepancies in coronary vessel sizing between quantitative coronary analysis (QCA) and intravascular ultrasound. That varies according to the vessel evaluated in an Egyptian population sample. To make appropriate adjustments to the size of the vessel during PCI (Percutaneous coronary intervention)

Patients and methods

This cohort study was conducted at Benha university hospital & National Heart Institute from January 2021 to August 2021. The patients were selected from those amenable to elective coronary angiography. Pa-

tients were examined clinically and underwent baseline workup, including renal function tests, complete blood count, random blood sugar, E.C.G., and echocardiographic examination. Patients who underwent coronary angiography and lesions were assessed by both QCA and IVUS. All participating cases in the study had written informed consent. and the study was approved by the Ethical Committee of Benha Faculty of Medicine.

Inclusion criteria:

Adult patients with stable angina (with evidence of ischemia) or unstable angina.

Exclusion criteria:

Patients not meeting the above inclusion criteria, hemodynamic instability, acute ST-elevation myocardial infarction (STEMI), renal insufficiency (serum creatinine> 1.5 mg/dl), dye allergy, and lesions located in the following sites were excluded; distal segment disease, saphenous vein grafts, and vessel disease of IVUS measurement less than 2.5 mm.

The angiographic assessment was done by both QCA and IVUS:

(1) Quantitative Coronary Analysis (QCA):

All coronary angiograms were performed and QCA data was analyzed using the same measurements. The QCA was calculated using (Philips or Siemens Medical System), as far as possible, the same anatomical view for the corresponding vessel to ensure standardization: the right anterior oblique caudal 30°/20° was used for the LCX; the right anterior oblique cranial was used for the LAD and the left anterior oblique cranial view was used for the RCA in each case. The QCA analysis was performed by experienced technicians supervised by an expert physician with identical angulations that best showed the stenosis at its most severe degree with minimal foreshortening and branch overlap. Computer software automatically calculated the luminal diameters. The QCA and IVUS analysis was performed independently by experts.

(2) Intravascular ultrasound (IVUS) assessment:

Imaging by Eagle Eye® - Philips Volcano Catheter. Following intracoronary infusion of nitroglycerine (100-200 micrograms) to minimize vasospasm, the rapid exchange IVUS catheter was introduced in the coronary over a standard 0.014" guidewire. Mechanical IVUS systems required infusion of heparinized saline to clear air bubbles inside the sheath covering the transducer before inserting the catheter in the guiding catheter. The IVUS catheter was advanced under fluoroscopy guidance approximately 10 mm distal to an anatomical landmark (i.e., side branch) and retracted slowly to straighten the catheter shaft which may have built some slack during insertion to minimize nonuniform rotation distortion (NURD) artifacts [8]. For the guidance of interventional procedures, the worst lesion site and relatively normal adjacent reference sites in end-diastolic frames were selected for analysis [8]. Based on the images depicted during the pullback of the transducer that had been inserted beyond the segment of interest, the lesion was defined as the image slice with the smallest lumen cross-sectional area. In the culprit's vessels, intravascular ultrasound was done before and after percutaneous coronary intervention.

Statistical analysis

Pre-coded data was entered on the computer using the "Microsoft Office Excel Software" program (365) for Windows. Data was then transferred to the Statistical Package of Social Science Software program, version 25 (SPSS) to be statistically analyzed (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, and interquartile range for quantitative variables and frequency and percentage for qualitative ones.

Results

The mean age of the studied patients was 54.65 ± 9.7 years. Regarding gender, there was a male predominance; (71%) were males. Also, diabetics, hypertensives, smoking, and dyslipidemia patients were (55.1%, 53.6 %, 59.4%, and 49.3% respectively) & history of PCI and CABG (Coronary artery bypass grafting) was (36.2 % and 21.7 % respectively) [Table 1]. Among 124 vessels affected, the left main artery was affected in 41.9% while LAD, LCX, and RCA represented 37.1%, 10.5%, and 10.5% of them respectively [Table 2].

There was a statistically significant difference between the luminal diameter of the left main artery measured by QCA in comparison to that by IVUS with differences ranging from -2.1 to 0.5 mm with a median of -0.8 mm [Table 3]. While in LAD the difference between the luminal diameter measured by QCA in comparison to that by IVUS with differences ranging from -1.3 to 0.5 mm with a median of -0.55 mm [Table 4]. Whereas the LCX luminal di-

Table 1

Demographic data and risk factors

	N=69	%
Gender: Male Female	 49 20	 71 29
Age (year): Mean ± SD Range	 54.652 ± 9.7 30 – 71	
Diabetes:	38	55.1
Hypertension:	37	53.6
Dyslipidemia:	34	49.3
Smoking:	41	59.4
Precious PCI:	25	36.2
Previous CABG:	15	21.7

Table 2

Distribution of the studied patients according to vessels affected

Number of vessels	N=124	%
Left Main artery (LM)	52	41.9%
Left anterior descending artery (LAD)	46	37.1%
Left circumflex descending artery (LCX)	13	10.5%
Right coronary artery (RCA)	13	10.5%

Table 3

Comparison between the luminal diameter of the left main artery (LM) measured by IVUS and that measured by QCA

	Luminal diameter by		Test	
	IVUS	QCA	t	p
Mean ± SD Range	4.909 ± 0.482 3.6 – 5.8	4.084 ± 0.544 2.3 – 5.4	17.284	<0.001**
r (95% CI)	0.507 (-0.147, 0.826)		p	<0.001**
The difference in luminal diameter measured by QCA and IVUS (mm)				
Median Range	-0.8 -2.1, 0.5			

t Paired sample t-test r interclass correlation coefficient CI confidence interval **p≤0.001 is statistically highly significant

Table 4

Comparison between the luminal diameter of the left anterior descending artery (LAD) measured by IVUS and that measured by QCA

	Luminal diameter by		Test	
	IVUS	QCA	t	p
Mean ± SD Range	3.87 ± 0.513 2.6 – 5.1	3.282 ± 0.468 2 – 4.5	13.418	<0.001**
r (95% CI)	0.646 (-0.189, 0.89)		p	<0.001**
The difference in luminal diameter measured by QCA and IVUS (mm)				
Median Range	-0.55 -1.3, 0.5			

t Paired sample t-test r Pearson correlation coefficient CI confidence interval **p≤0.001 is statistically highly significant.

ameter was measured by QCA in comparison to that by IVUS with differences ranging from -1.5 to 0.25 mm with a median of -0.4 mm [Table 5]. Whilst the difference between the luminal diameter of RCA was measured by QCA in comparison to that by IVUS with differences ranging from -0.8 to -0.2 mm with a median of -0.5 mm [Table 6]. So, the discrepancy between luminal diameter measured by IVUS and QCA (median difference in measures by QCA and IVUS in the left main artery, LAD, LCX and RCA were -0.8, -0.55, -0.4, and -0.5 respectively). On pairwise comparison, the difference is significant between the left main artery and each other vessel. Also, there was a statistically significant difference between the studied vessels regarding the presence of difference >0.75 mm between luminal diameter measured by IVUS and QCA (Difference >0.75 mm in the left main artery, LAD, left circumflex and RCA were 55.8%, 21.7%, 30.8%, and 15.4% respectively) [Table 7].

Table 5

Comparison between the luminal diameter of left circumflex artery (LCX) measured by IVUS and that measured by QCA:

	Luminal diameter by		Test	
	IVUS	QCA	t	p
Mean ± SD Range	3.589 ± 0.532 2.8 – 4.7	3.004 ± 0.462 2.3 – 4	5.174	<0.001**
r (95% CI)	0.572 (-0.266, 0.876)		p	0.012*
The difference in luminal diameter measured by QCA and IVUS (mm)				
Mean ± SD Range	-0.4 -1.5, -0.25			

t Paired sample t-test r Pearson correlation coefficient CI confidence interval **p≤0.001 is statistically highly significant

Table 6

Comparison between the luminal diameter of right coronary artery (RCA) measured by IVUS and that measured by QCA:

	Luminal diameter by		Test	
	IVUS	QCA	t	p
Mean ± SD Range	3.539 ± 0.512 2.7 – 4.3	3.062 ± 0.429 2.2 – 3.5	10.458	<0.001**
r (95% CI)	0.739 (-0.101, 0.945)		p	<0.001**
The difference in luminal diameter measured by QCA and IVUS (mm)				
Mean ± SD Range	-0.5 -0.8, -0.2			

t Paired sample t-test r interclass correlation coefficient CI confidence interval **p≤0.001 is statistically highly significant

Table 7

Comparison between difference >0.75 mm between luminal diameters of different arteries measured by IVUS and QCA

Difference	Arteries				Test	
	LM	LAD	LCX	RCA	χ^2	p
	N=52(%)	N=46(%)	N=13(%)	N=13(%)		
≤0.75 mm **>0.75 mm**	23 (44.2) 29 (55.8)	36 (78.3) 10 (21.7)	9 (69.2) 4 (30.8)	11 (84.6) 2 (15.4)	MC	<0.001**
Difference: Median Range	-0.8¥ -2.1, 0.5	-0.55 -1.3, 0.5	-0.4 -1.5, -0.25	-0.5 -0.8, -0.2	26.179	<0.001**

MC Monte Carlo test KW Kruskal Wallis test **p≤0.001 is statistically highly significant ¥group responsible for significant difference

Additionally, there was a statistically significant difference between the left main and non-left main arteries affected regarding the difference between luminal diameter measured by IVUS and QCA (median difference in the left main artery and non-left main artery were -0.8 and -0.5 respectively). Also, the difference between left main and non-left main arteries affected regarding the presence of difference>0.75 mm between luminal diameter measured by IVUS and QCA (Difference>0.75 mm in the left main artery, and non-left main artery affected was 55.8%, and 22.2% respectively) [Table 8].

Table 8

Comparison between discrepancy >0.75 mm between luminal diameters of left main and non-left main measured by IVUS and QCA:

Discrepancy	Arteries		Test	
	Left main	Non-left main	χ^2	p
	N=52(%)	N=72 (%)		
≤0.75 mm **>0.75 mm**	23 (44.2) 29 (55.8)	56 (77.8) 16 (22.2)	14.697	<0.001**
Difference: Median Range	-0.8 -2.1, 0.5	-0.5 -1.5, 0.5	-5.062	<0.001**

χ^2 Chi-square test Z Mann Whitney test

Discussion

The current study involved 69 patients who were selected from those referred to coronary elective coronary angiography. Their gender, risk factors, laboratory data, and angiographic results were collected and statistically analyzed. In our study, we used QCA and IVUS to assess the luminal diameter of each coronary vessel to reveal differences between both.

In our study, the studied patients were 71% males with a mean age of 54.7 ± 9.7 years. The main risk factors were smoking (59.4%), systemic hypertension (53.6%), diabetes mellitus (55.1%), dyslipidemia (49.3%) with a history of PCI (36.2 %), and CABG (21.7 %). This is consistent with Goel et al. study [9] which was included (87%) males with a mean age of 57.5+9.8 years with systemic hypertension (53%), dyslipidemia (46.1%), diabetes mellitus (34%), and smoking (32%) as risk factors. In addition, De la Torre Hernandez et al. study [10] included (76%) males with a mean age of 66.5 ± 11.0 years with systemic hypertension (63.1%), dyslipidemia (65.9%), diabetes mellitus (35.8%), and smoking (25.1%) as risk factors with history of PCI (29.6 %) and CABG (2.8%). Furthermore, Jen-Hsiang Wang et al. study [11] enrolled (80%) males with mean age 68±8 years, and risk factors of smoking (55.2%), systemic hypertension (59 %), diabetes mellitus (54%), dyslipidemia (46.2%) with a history of PCI (25.3 %) and CABG (5.6 %). Moreover, Fernandes et al. study [12] studied patients were (54%) males with an average age of 61 ± 13 years, (48%) had dyslipidemia, (27%) were smokers, (62%) had systemic hypertension, and (17%) had diabetes.

Our study studied sixty-nine patients with lesions involved Left main in 52 cases (41.9%), LAD in 46 cases (37.1%), followed by LCX in 13 cases (10.5%), and RCA in 13 cases (10.5%). And the discrepancy between luminal diameter measured by IVUS and QCA was calculated. Left main luminal diameter was 4.9 ± 0.48 by IVUS versus 4.1 ± 0.5 by QCA, LAD luminal diameter was 3.87 ± 0.5 by IVUS versus 3.3 ± 0.46 by QCA, LCX luminal diameter was 3.6 ± 0.5 by IVUS versus 3.0 ± 0.46 by QCA and RCA luminal diameter was 3.5 ± 0.5 by IVUS versus 3.0 ± 0.4 by QCA. The median differences in measures of QCA

and IVUS in the left main artery, LAD, LCX, and RCA were -0.8, -0.55, -0.4, and -0.5 respectively. And the presence of difference >0.75 mm between luminal diameter measured by IVUS and QCA (Difference >0.75 mm in the left main artery, LAD, LCX, and RCA was 55.8%, 21.7%, 30.8%, and 15.4% respectively). Similarly, in Goel et al. study [9] assessed 186 cases of Left main with luminal diameter by IVUS was 4.33 ± 0.32 versus QCA which was 3.89 ± 0.25. And the assessed 177 cases of LAD with luminal diameter by IVUS was 3.61 ± 0.21 versus QCA diameter was 3.36 ± 0.28. And the assessed 44 cases of LCX with luminal diameter by IVUS was 3.31 ± 0.16 versus QCA diameter was 2.85 ± 0.27. Also, De la Torre Hernandez et al. study [10] in which 179 cases of the left main lesion were assessed and the luminal diameter by IVUS was 4.2 ± 0.7 versus QCA diameter was 3.9 ± 0.8. In addition, Jen-Hsiang Wang et al. study [11] studied LAD lesions of 30 patients, The mean reference diameter of the LAD proximal segment by QCA was 3.21 mm, and IVUS was 3.40 mm. The mean reference diameter of the LAD middle segment by QCA was 3.00 mm and IVUS was 3.28 mm. Moreover, Fernandes et al. study [12] studied 56 patients with a total of 63 stenotic coronary lesions and assessment of reference segment luminal diameter, which was 2.83 ± 0.56 mm by angiography versus 3.45 ± 0.69 mm by IVUS.

On the other hand, Takagi et al. study [13] enrolled 427 consecutive patients, mainly males' patients (93.9%) with a mean age of 63.75± 10.0 years with systemic hypertension (56.8%), dyslipidemia (59.9%), diabetes mellitus (19.4%), smoking (26.2%), previous CABG (12.6%) and previous PCI (48%) as risk factors. They underwent PCI with intravascular ultrasound (IVUS)-guidance. The minimum stent diameter (MSD) was measured using QCA (MSDQCA) and IVUS (MSDIVUS) analysis. The lesions were assessed were 162 lesions in LAD, 70 in LCX, and 77 in RCA. The mean MSDQCA and MSDIVUS were 3.04 ± 0.49 mm and 2.68 ± 0.47 mm, respectively. And concluded that the MSDQCA is more likely to overestimate in the LCX than in the LAD, particularly when the MSDIVUS is 2.5 mm. Therefore, it is recommended that be less aggressive in oversizing balloons and stents based on QCA for LCX or small vessel intervention.

There was a difference > 0.75 mm between the luminal diameter measured by IVUS and QCA (Difference > 0.75 mm in the left main artery, LAD, LCX, and RCA were 55.8%, 21.7%, 30.8%, and 15.4% respectively). In other words, there was a presence of a difference > 0.75 mm between the luminal diameters measured by IVUS and QCA (Difference > 0.75 mm in the left main artery and non-left main artery affected were 55.8%, and 22.2% respectively). On the contrary, Takagi et al. study[13] found that the difference between MSDQCA and MSDIVUS of > 0.75 mm was more frequently observed in the LCX rather than in the LAD (7.4% in the LAD vs. 24.3% in the LCX, p = 0.001). The discrepancy between the MSDQCA and MSDIVUS for the LCX was larger than for the LAD and tended to be larger than for the RCA (13.3% vs. 18.5%, p = 0.05 and 18.5% vs. 14.5%, p = 0.17). Which could support the strategy to downsize devices in the LCX to reduce the occurrence of coronary dissection and rupture.

Limitations

Our study has some limitations. The size of the population sample was relatively small and not randomized. Larger, multi-centric studies should be performed to confirm our results. Our study population had only 29% females, thereby limiting the generalizability of the results. The measurements were not validated by an external core laboratory, which could have allowed some intraobserver bias. In addition, further research would be required to validate our results.

Conclusion

Coronary lesions were underestimated by QCA in comparison to IVUS regarding luminal diameter (Media to media), especially the left main (LM).

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

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This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

Author contribution

The authors contributed equally to the study. The authors read the ICMJE criteria for authorship and approved the final manuscript.

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SHORT REPORT

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Modeling of threats in the sphere of medical data storage

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Abstract

In medical institutions of various levels, a large amount of data is stored in electronic form, to ensure the safety of which are presented with special requirements. Ensuring the safety of the storage of medical data should begin with an analysis of existing threats. This article provides a model of threats in the area of data storage, which includes the following components: comunicative, spatial and destructive threat. It is shown that, to date, communicative and spatial threats have minor rates, which can be neglected. The destructive threat is considered in more detail, its components are described. Recommendations for the development of medical data storage systems are given.

Keywords

Data storage, Recommender system, Medical records, Database

Imprint

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Nowadays, in medical institutions a large amount of data is stored in electronic form. Most often, medical data on the patient includes: age, gender, anthropometric data, information on past and chronic diseases, the current diagnosis, the plan for further therapy, etc., which are obtained from professional medical workers. Thus, there are special requirements for storing medical data.

Ensuring the safety of the storage of medical data should begin with an analysis of existing threats. In accordance with [3], three types of storage threats are distinguished: communicative, spatial and destructive, which can be presented in the form of the following mathematical model:

$$U = c*UP + b*UK + a*UD,$$

where U is the total probability of a threat in the storage area,
UP is the probability of a spatial threat,
UK the probability of communicative threats,
UD the probability of a destructive threat,
a, b, c - specific weight ratios of types of threats.

The proposed mathematical model of threat in the storage area is applicable for information systems of various levels that may include both one PC in a private medical office and a computer local network of a large medical institution.

The total probability of a threat in the storage area will be in the interval of boundary values from 0 to 1. However, the boundary values can only be achieved in the limit, these values are not achievable in real life. The zero threat can only be in the absence of an information system to which a mathematical model of threats is applied. A value of the total probability of threats in the sphere of data storage equal to 1 means that the information system at the time of the assessment is no longer workable.

Specific weight coefficients are determined based on the analysis of statistical data obtained as a result of collecting information on the number of incidents according to the types of threats during a predetermined significant period of time. For medical institutions significant period of time can be set from the moment the organization of data storage in electronic form. Obviously, the sum of the specific weight coefficient values should be equal to 1 or 100%:

$$a+b+c=1 \text{ (or } 100\%).$$

This approach to the boundary conditions of the mathematical model of the occurrence of threats in the storage area will allow the total probability to remain in the specified limits.

The spatial threat is a threat of the repository overflow due to the constantly growing volume of the data being stored. The probability of occurrence of the spatial threat is determined by the availability of free space on the disks of medical institutions and the volume of stored data.

Communicative threat represents the lack of access to stored data. The probability of the communicative threat is determined based on the statistical

analysis of the reliability of lines and communications devices.

To date, there is no uniform centralized medical data storage system, which would have had information about the state of health of the country's population and to which access from any medical institution would be organized. Since all medical data is stored locally in separate medical institutions, the communicative and spatial threats are very insignificant in view of the fact that they are localized within each individual institution. In addition to minor rates of probabilities of the spatial and communicative threats occurrence, the values of the specific weight coefficients are also insignificant. As a result, the total probability of a threat in the storage area of medical data is reduced to determine the likelihood of a destructive threat, since the communicative and spatial threat can be neglected.

Destructive threat arises due to external influence on the data, resulting in a partial or complete loss of information.

In accordance with [3] destructive threat includes the following types of threats: software, virus, encryption, hacker's, physical and user's, they all can be presented in a graphical model.

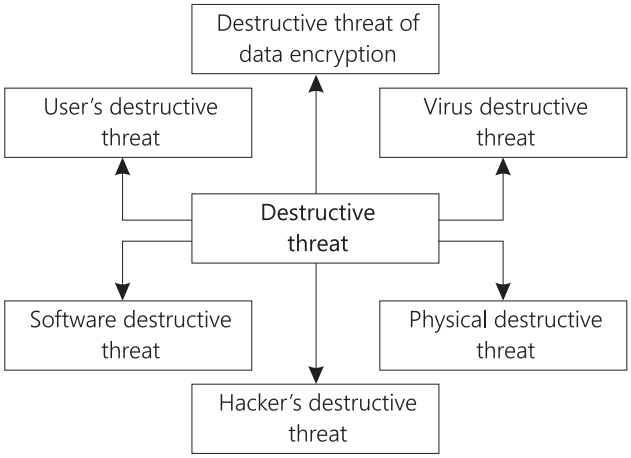

Figure 1. Destructive threat types

The probability of a destructive threat may also be presented in the form of a mathematical model:

$$U_д = a_s*UD_s + a_v*UD_v + a_c*UD_c + a_{hc}*UD_{hc} + + a_{hw}*UD_{hw} + a_u*UD_u,$$

where UD_s is a software destructive threat,
UD_v is a virus destructive threat,
UD_c is a destructive threat of data encryption,
UD_{hc} is a hacker's destructive threat,
UD_{hw} is a physical destructive threat,
UD_u is a user's destructive threat,

a_s, a_v, a_c, a_{hc}, a_{hw}, a_u – specific weight coefficients of a destructive threat component.

In turn, the probability of the occurrence of a destructive threat also lies in the range from 0 to 1, but cannot reach the boundary conditions in real life. This is explained by the fact that the 0 meaning implies the complete absence of stored data, and the value equal to 1 indicates that at the time of the assessment, the data is destroyed due to the occurrence of destructive threat.

Specific weight coefficients of the destructive threats components are determined based on a statistical analysis of incidents for the selected significant period of time. It is also evident that to meet the boundary conditions for the destructive threat probability the sum of values of components specific weight coefficients must be equal to 1, or 100%:

$$a_s + a_v + a_c + a_{hc} + a_{hw} + a_u = 1 \text{ (or 100\%)}$$

The software destructive threat arises due to a malfunction of a medical information system or a program that leads to damage or complete data deletion, as a result of which it becomes impossible to work with information.

Failures in the work of a medical information system or a program may occur as a result of a disconnection of electricity, failure of any physical component of the computer system as a whole, errors or deficiency of software developers. As a result, occurs any failure in the data processing, which leads to distortion or loss of data.

Virus destructive threat arises as a result of penetration into a computer system of a virus or malicious program, which can both cause damage or delete files from a hard disk and change data in it.

The destructive threat of data encryption is a kind of a virus destructive threat, since it has the same ways to penetrate the computer system of a medical institution. However, in relation to health facilities the destructive data encryption is highlighted as a particular type of threat, as data not deleted or corrupted there, but encrypted for subsequent commercial sale of decryption algorithms, which actually is a financial cyber crime.

For virus destructive threat and destructive data encryption threat, we can enumerate the following paths of infecting:

a) connecting an external information storage device (when the virus penetrates the system when connected to a computer external storage devices);

b) connecting to the Internet (when the virus enters the device through the downloaded infected file, visiting the infected site, opening a letter with a virus in email).

Hacker's destructive threat is a deliberate penetration into a computer system with the aim of illegal information downloading, as well as damage, distortion or complete data deletion. In accordance with the Federal Law No. 152 «On Protection of Personal Data», a separate task is to ensure the protection of personal data stored in the databases of medical institutions. Therefore, great attention should be paid to protection from hacker attacks.

The physical destructive threat is a threat to the failure of the internal storage device and any component of the computer whose disruption can lead to the failure of the internal storage device, as a result of which the partial or complete loss of medical data occurs.

User's destructive threat arises due to an error of a user or operator, as a result of which the data is deleted or distorted due to inattention, incorrectly accepted solutions or targeted action of the attacker.

To eliminate the user's threat is possible only at 100% process automation. However, it is impossible to perform it 100%, since at the initial stage, even for an existing automated system, the initial data is still set by the user and completely eliminate the user's actions is impossible. In case if at the stage of data input occurs uncorrected unnoticed or just minor error, then during subsequent processing of the data may be a critical situation which can lead to errors in the work of medical personnel (e.g., wrong prescription medications and others). Thus, it can be concluded that the qualification of the user, which works with medical data should be high enough.

Conventionally, the user's destructive threat can be divided into the following types:

1. Data input error occurs as a result of casual typo when entering data. Due to any circumstances, the operator does not notice the error and continues entering. In this case, a purely human factor is triggered, which cannot be completely eliminated.

2. The interpretation error occurs as a result of an incorrect understanding by the operator of the information he receives for input. Quite often, the operator has an insufficient conceptual apparatus or a terminological dictionary, as a result of which the information entered is distorted by the operator unconsciously. These incidents can be avoided due to the training and systematic certification procedures for operator in order to form the unified concept of identifying medical information.

3. The deliberate input of incorrect data arises as a result of the targeted desire of the operator to distort the reliable information introduced into the system. It is possible to exclude this threat by checking the reliability of the employee at the employment stage of the organization's internal security or personnel service. In addition, it is impossible to exclude the deliberate input of distorted or incorrect data in order to cause harm to patients or for obtaining own economic benefits.

4. Intentional theft or removal of data typically occurs as a result of self-serving purposes. This threat is eliminated by backing up information on protected storage devices.

5. Unintentional data deletion occurs as a result of the erroneous actions of the operator. Incorrect user's actions, leading to accidental removal of any amount of information, are a consequence of the human factor.

Today, the destructive threat is the greatest danger to storing medical data, since it is difficult to predict enough. The occurrence of spatial threats with a regular systemic analysis of methods for storing medical data can be foreseen. Communicative threats do not lead to loss of medical data, but only temporarily restrict access to them. At the same time, to predict the user's behavior, the system failure, unauthorized penetration and failure of the equipment is almost impossible. Anti-virus software also does not give a hundred% guarantee of data security. However, properly organized backup of medical data allows you to minimize the consequences of the arising destructive threats.

Thus, there exists a need to create a unified centralized information system for the storage of medical data, in which the organization of protection against destructive threats will have a complex systematic nature. To collect all medical information on the patient in one place, it is proposed to create personal electronic health cards (PEHC) The PEHC data can be integrated into medical recommender systems (MRSs). Based on the analysis of information on the patient, MRS will send data to the user interface, the data most suitable for a particular patient, which will solve the problem of the cold start, one of the most common reasons for reducing the relevance of recommendations and, accordingly, the quality of the recommender systems.

It should also be taken nto account that when organizing a single centralized storage of medical data, integrated with one or more medical recommender systems, it is necessary to provide access to the repository to all employees of medical institutions according to their profile of activities, which in turn sharply increases the rates of communicative and spatial threats.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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