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THE STUDY OF ANTIGENOTOXIC ACTIVITY OF THE MEDICINAL PLANTS INFUSIONS OF TRANS-ILI ALATAU

Due to growing number of factors causing a hazard effect to nature, the search for protectors becomes urgent in environment. Using the bioluminescent test (lux-biosensor), genotoxic, oxidative, antigenotoxic and antioxidant activities of sage (Salvia officinalis), oregano (Origanum vulgare), chamomile (Matricaria chamomilla) and yarrow (Achillea millefolium) have been studied. We used genetically modified E. coli strains: E. coli MG 1655 (pColD-lux), E. coli MG 1655 (pRecA-lux), E. coli MG 1655 (pSoxS-lux), E. coli MG 1655 (pKatG-lux). The operon MG 1655 is responsible for the work on luciferase and the provision of bioluminescence, which applied in this test for its reporter function. The infusions investigated under various methods of preparation (concentrated, diluted and phyto-tea) did not reveal genotoxic and oxidative activity. The induction factor of the SOS-response in all strains is statistically significant, not exceeding the level of the negative control (distilled water). The combined effect of medicinal plants with mutagen 4-nitroquinoline 1-oxide (4-NQO) and oxidants paraquat with hydrogen peroxide did not show a statistically significant decrease in SOS responses to the pColD-lux, pRecA-lux, pKatG-lux pSoxS-lux sensors, induced by 4-NQO, hydrogen peroxide and paraquat. The exception alerted by sage. Concentrated sage infusion, prepared according to the recipe, and sage phyto-tea statistically significantly reduce the induction factor of the pKatG-lux biosensor SOS response ($p < 0.001$). The level of inhibition depended on the type of infusion. Concentrated infusion and phyto-tea showed a strong antioxidant effect against hydrogen peroxide, while inhibition was 43.6% and 46.8%, respectively. Diluted sage infusion showed a moderate antioxidant effect with an inhibition rate of 29.2%. Thus, using a bioluminescent test, antioxidant activity of the concentrated infusion and phyto-tea of sage are released using the pKatG-lux biosensor. It can be assumed, that the sage infusion contains biologically active substances that are capable of both inactivating hydrogen peroxides and organic peroxides. Considering that oregano, chamomile and yarrow contain many biologically active substances, but the test did not reveal antigenotoxic and antioxidant activity. Therefore, it can be concluded that the required amount of biologically active substances for detect activity is not extracted during the preparation of the infusion.

Key words: lux-biosensors, Salvia, Origanum, Matricaria, Achillea, antioxidant.

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Іле Алатауының дәрілік өсімдіктерінің тұнбаларын антигенотоксикалық белсенділікке зерттеу

Қоршаған ортада қауіпті экологиялық факторлардың көбеюіне байланысты, ксенобиотиктермен индуцирленетін токсикалық және экологиялық әсерлерді түзеу үшін табиғи эффективті протекторларды табу өзекті мәселе болып табылады. Биолюминисцентті тест (lux-биосенсор) көмегімен сәлбен (Salvia), киікоты (Origanum), түймедақ (Matricaria) және мыңжапырақ (Achillea) тұнбаларының генотоксикалық, оксидантты, антигенотоксикалық белсенділіктері зерттелді. Жұмыста E. coli: E. coli MG 1655 (pColD-lux), E. coli MG 1655 (pRecA-lux), E. coli MG 1655 (pSoxS-lux), E. coli MG 1655 (pKatG-lux) генетикалық модификацияланған штаммдары қолданылды. Аталған MG 1655 опероны люциферазалардың жұмысына жауап береді және бұл тестте репортерлі міндет атқаратын биолюминисценцияны қамтамасыз етеді. Зерттелінетін тұнбалар әртүрлі даярлау тәсілдерінде (қою, сұйылтылған және фито-шәй) генотоксикалық және оксидантты белсенділік көрсеткен жоқ. SOS-жауапты индуцирлейтін фактор барлық штаммдарда теріс бақылаудың (дистилдинген су) деңгейінен статистикалық маңызды түрде асқан жоқ. Дәрілік өсімдіктердің тұнбалары мутаген 4-нитрохинолин 1-оксид (4-HXO) және оксиданттар паракват, сутегінің тотығымен бірге әсер еткенде pColD-lux, pRecA-lux, pKatG-lux және pSoxS-lux сенсорларында 4-HXO, сутегінің тотығы және паракватпен индуцирленген SOS-жауаптың статистикалық маңызды түрде төмендеуі байқалған жоқ. Тек сәлбен тұнбалары ерекшелік көрсетті. Рецепт бойынша дайындалған сәлбеннің қою тұнбасы және фито-шәй pKatG-lux биосенсорының SOS-жауапты индукциялау факторын статистикалық маңызды түрде ($p < 0,001$) төмендетті. Сонымен қатар ингибирлеу деңгейі тұнба түріне тәуелді болды. Сәлбеннің қою тұнбасы және шәйі сутегі тотығына қарсы күшті антиоксидантты әсер көрсетті, ингибирлеу сәйкесінше 43,6% және 46,8% құрады. Ал сәлбеннің сұйылтылған тұнбасы, ингибирлеу деңгейі 29,2%, орташа антиоксидантты әсер берді. Осылай, биолюминисцентті тест көмегімен сәлбеннің қою тұнбасы мен фито-шәйінің антиоксидантты белсенділігі pKatG-lux биосенсоры арқылы көрсетілді. Сәлбен тұнбаларының құрамында, гидрототықтарды және органикалық пероксидтарды инактивациялауға қабілетті биологиялық белсенді заттар бар деген болжам жасауға болады. Киікоты, түймедақ және мыңжапырақ құрамында көптеген биологиялық белсенді заттар бар екенін ескере отырып, бірақ, тест антигенотоксикалық және антиоксидантты белсенділік анықтамағанына сүйеніп, тұнба дайындаған кезде, белсенділік анықтау үшін, биологиялық белсенді заттардың керекті мөлшері алынбайды деген болжам айтуға болады.

Түйін сөздер: lux-биосенсорлар, Salvia, Origanum, Matricaria, Achillea, антиоксидант.

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Изучение антигенотоксической активности настоев лекарственных растений Заилийского Алатау

В связи с увеличением экологически опасных факторов в окружающей среде становится актуальным поиск эффективных протекторов природного происхождения для коррекции токсических и генетических эффектов, индуцируемых ксенобиотиками. С помощью

биолюминесцентого теста (lux-биосенсор) были изучены генотоксическая, оксидантная, антигенотоксическая и антиоксидантная активности настоев шалфея (Salvia officinalis), душицы (Origanum vulgare), ромашки (Matricaria chamomilla) и тысячелистника (Achillea millefolium). В работе были использованы генетически модифицированные штаммы E. coli: E. coli MG 1655 (pColD-lux), E. coli MG 1655 (pRecA-lux), E. coli MG 1655 (pSoxS-lux), E. coli MG 1655 (pKatG-lux). Данный оперон MG 1655 отвечает за работу люцифераз и обеспечивает биолюминесценцию, используемую в данном тесте в качестве репортерной функции. Исследуемые настои при различных способах приготовления (концентрированный, разбавленный и фито-чай) не проявили генотоксической и оксидантной активности. Фактор индукции SOS-ответа у всех штаммов статистически значимо не превышал уровня отрицательного контроля (дистиллированная вода). При совместном воздействии настоев лекарственных растений с мутагеном 4-нитрохинолина 1-оксидом (4-НХО) и оксидантами паракватом и перекисью водорода не наблюдалось статистически значимого снижения SOS-ответов на сенсорах pColD-lux, pRecA-lux, pKatG-lu хи pSoxS-lux, индуцированных 4-НХО, перекисью водорода и паракватом. Исключение составили настои шалфея. Концентрированный настой шалфея, приготовленный согласно рецептуре, и фито-чай статистически значимо снижали фактор индукции SOS-ответа биосенсора pKatG-lux ($p < 0,001$). При этом уровень ингибирования зависел от вида настоя. Концентрированный настой и чай шалфея проявили сильный антиоксидантный эффект против перекиси водорода, при этом ингибирование составило соответственно 43,6% и 46,8%. Разбавленный настой шалфея дал умеренный антиоксидантный эффект с уровнем ингибирования 29,2%. Таким образом, с помощью биолюминесцентного теста показана антиоксидантная активность концентрированного настоя и фито-чая шалфея с помощью биосенсора pKatG-lux. Можно предположить, что в составе настоев шалфея содержатся биологически активные вещества, способные инактивировать гидроперекиси и органические пероксиды. Учитывая, что душица, ромашка, тысячелистник содержат множество биологически активных веществ, а тест не выявил антигенотоксической и антиоксидантной активности, то можно предположить, что при приготовлении настоев не извлекается нужное количество биологически активных веществ для выявления активности.

Ключевые слова: lux-биосенсоры, Salvia, Origanum, Matricaria, Achillea, антиоксидант.

Introduction

Most of the chemical pollutants of the environment are capable of genotoxic, mutagenic and carcinogenic effects on organisms. The genotoxicity of any factor is maintained in direct and indirect effects on DNA [1]. The mediated effect on DNA may be due to the activation or inhibition of various processes in the cell, for example, induction of intracellular free radicals and inhibition of the activity of cellular repair systems [2, 3]. As a rule, a wide range of genetic effects are recorded in genetic toxicology using methods for determining the induction of a SOS response in bacterial cells, reparative synthesis and DNA breaks in mammalian cells [1].

It is impossible to escape human contact with genetically dangerous factors in everyday life. Therefore, the search for effective protectors, antigenotoxicants and antimutagens, becomes extremely important. Most of the biologically active substances (BASs) of natural origin, such as vitamins, vegetable flavonols, phytohormones, polypeptides, amino acids, etc., have such protective properties. Many BASs have antioxidant properties and can increase the body's resistance to various genotoxicants. In recent years, interest in the study of medicinal plants as promising sources of antimutagenic active substances has increased significantly, due to their low toxicity and allergenicity, complex effects on the body and the possibility of long-term use without side effects [4-6]. Biologically active compounds can affect the genotoxic factor simultaneously in several different ways, which significantly increases the effectiveness of the antigenotoxicant itself [7]. Therefore, the search for effective protectors of natural origin for the correction of genetic effects induced by xenobiotics widely used by humans, as well as prevention means for the protection of hereditary structures, is an extremely important task.

Flora of Kazakhstan has about 6000 species of higher strata, of which 1406 are medicinal. In Kazakhstan, only 230 species are actually used in official medicine [8]. A survey conducted by us in August 2017 showed that the population knows just over 60 species of medicinal plants used for treatment and nutritional purposes. The flora of the Ile Alatau mountain range includes over 800 plant species, of which 117 species are medicinal. In phytochemical terms, the medicinal plants of the local flora contain most of the known classes of biologically active substances. Among them are predominant species containing flavonoids and their derivatives (60% of species), alkaloids (42%), organic and phenolic acids

(34%), vitamins (32%), tannins (29%), coumarins (25%) and others. According to the phytochemical composition, medicinal plants of Kazakhstan have a very wide spectrum of pharmacological action [8].

Plants of the genera *Matricaria* and *Achillea* of the *Asteraceae* family are used as anti-inflammatory, antiviral, antibacterial, wound healing, sedative, antioxidant, detoxifying, anesthetic, hepatoprotective, and antiseptic [8-10]. Plants genera of the *Origanum* and *Salvia* of the *Lamiaceae* family have anti-inflammatory, antioxidant, sedative, antibacterial, wound healing, tonic, antiseptic effects, and are used in diseases of the upper respiratory tract and the gastrointestinal tract [8, 11, 12].

The purpose of this study was to study the genotoxic and antigenotoxic activity of infusions of sage (*Salvia officinalis L.*), oregano (*Origanum vulgare L.*), chamomile (*Matricaria chamomilla L.*) and yarrow (*Achillea millefolium L.*) grown in Trans-Ili Alatau, using *lux*-biosensors.

Materials and methods

Infusions of sage (*Salvia officinalis* L.), oregano (*Origanum vulgare* L.), chamomile (*Matricaria chamomilla* L.) and yarrow (*Achillea millefolium* L.) were tested for genotoxic and antigenotoxic activity.

Were used 3 types of infusion of medicinal plants: concentrated – according to the recipe; diluted – concentrated infusion, diluted 2 times; tea – 1 spoon of a medicinal plant raw was poured with boiling water and infused for 15 minutes.

Distilled water served as negative control. 4-nitroquinoline 1-oxide (4-NQO, $C_9H_6N_2O_3$) was used as a genotoxicant (positive control), and paraquat ($C_{12}H_{14}C_{12}N_2$) and hydrogen peroxide (H_2O_2) were used as oxidative substances (positive control).

We used genetically modified *E. coli* strains: *E. coli* MG 1655 (pColD-*lux*), *E. coli* MG 1655 (pRecA-*lux*), *E. coli* MG 1655 (pSoxS-*lux*), *E. coli* MG 1655 (pKatG-*lux*) [13-15]. This operon is responsible for the luciferase function and provides the bioluminescence used in this test as a reporter function. Strains courtesy of G.B. Zavilgelsky and I.V. Manukhov (State Research Institute of Genetics, Moscow).

For detection of substances that induce DNA damage, the promoters pColD and pRecA were used. To activate these promoters, 4-nitroquinoline 1-oxide (4-NQO) at a concentration of 75.0 μg/ml was used. For the detection of substances that induce oxidative stress in the cell, the PkatG and PsoxS promoters were used. The PkatG promoter (protein-activator OxyR) specifically reacts to hydrogen peroxide and organic peroxides, and the promoter PsoxS (protein-activator SoxR) – to superoxide ion radicals [15]. To activate the pKatG promoter, hydrogen peroxide at a concentration of 0.01 μg/ml was used, and for activation of the PSoxS promoter, paraquat (1,1'-dimethyl-4,4'-dipyridylium dichloride) at a concentration of 10.0 μg/ml was used. Bacteria were grown in Luria-Bertani broth (LB) containing 100 μg/ml ampicillin. The overnight culture was diluted to a concentration of 10^7 cell/ml in fresh broth and grown at 37°C for 2–3 h. Aliquots of this culture (180-190 μl each) were transferred to sterile cells in the strip plates and added to them depending on experimental variant of 20 μl of the tested infusion and / or 20 μl of oxidative stress inducer (except control cells), while 40.0 μl of distilled water was added to the control wells.

During the evaluation of genotoxic and oxidative activity, 20 μl of distilled water and 20.0 μl of infusion or oxidative stress inducers were added separately to aliquots of the culture. During the evaluation of the antigenotoxic and antioxidant potential, aliquots of the culture were jointly added with 20.0 μl of infusion and oxidative stress inducers.

They were incubated at certain time intervals: for pColD-*lux* – 90 minutes, pRecA-*lux* and pSoxS-*lux* – 60 minutes, for pKatG-*lux*– 45 minutes. The luminescence level of bacteria was measured on a LuMate 4400 microplate luminometer (Awareness Technology, USA) and expressed in relative light units (RLU). A measure for genotoxicity is the induction factor (I), defined as the ratio of the intensity of the glow of a *lux*-biosensor suspension containing the test compound (L_c), to the intensity of the glow of a *lux*-biosensor control suspension (L_k). The indicator of antigenotoxic potential, or protective activity (AA,%) was calculated by the formula $AA = \left(1 - \frac{I_a}{I_p}\right) \times 100$, where I_a is the induction factor of the SOS response by the test exposure in the presence of a protector; I_p is the induction factor of the SOS response by the test exposure; 100 – coefficient for conversion to percent. The antigenotoxic effect was considered as moderate when inhibition of the induction factor of the SOS response of genotoxicants by 25–40%, high at 40%, with less than 25%, the effect was considered weak and did not recognize the result as positive.

All experiments were performed in two independent replicates. As a characteristic of the protector activity of the studied concentration of the substance, the average value of AA was used throughout the entire measurement time.

Results

Study of antigenotoxic and antioxidant activity of infusions of sage (Salvia officinalis L.) and oregano (Origanum vulgare L.)

With the bioluminescent test (*lux*-biosensors), the ability of sage and oregano infusions to protect *E. coli* MG 1655 (pColD-*lux*) and *E. coli* MG 1655 (pRecA-*lux*) strain from DNA damage under the action of 4-NQO, inactivate superoxide anion was studied under the action of paraquat on the biosensor strain *E. coli* MG 1655 (pSoxS-*lux*), inactivate hydroperoxides and organic peroxides under the action of hydrogen peroxide on the biosensor strain *E. coli* MG1655 (pKatG-*lux*).

In studies, infusions of sage (Table 1) did not show genotoxic and prooxidant activity. The induction factor of the SOS response of the pColD-*lux* and pRecA-*lux* biosensors when exposed to the concentrated sage infusion was 0.93 and 0.88, respectively; diluted infusion – 0.93 and 0.90; phyto-tea – 0.98 and 0.93. The induction factor for the SOS response of the pKatG-*lux* and pSoxS-*lux* biosensors after exposing to the concentrated sage infusion was 1.77 and 1.03, respectively; diluted infusion – 1.23 and 1.06; phyto-tea – 1.37 and 1.06.

Table 1 – Induction of luminescence in bacterial lux-biosensors with biologically active substances of infusions and sage phyto-tea

Experiment variance	Induction of luminescence* in bacterial *lux*-biosensors			
	E.coli MG1655 (pColD-*lux*)	*E. coli* MG1655 (pRecA-*lux*)	*E. coli* MG1655 (pKatG-*lux*)	*E. coli* MG1655 (pSoxS-*lux*)
Negative control	447.19±30.92	17373.06±1123.99	1406.69±138.46	3448.00±318.69
Positive control	13387.56±2530.85▪	150444.44±21210.97▪	59161.69±9198.45▪	22841.00±5633.88▪
Concentrated sage infusion	414.81±61.04	15356.00±1216.60▪◊	2495.88±526.45▪◊	3562.63±251.22
Diluted sage infusion	416.25±76.25	15690.19±801.93▪◊	1724.38±187.84▪◊	3637.94±273.07
Sage phyto-tea	438.31±87.16	16208.25±1231.54▪◊	1927.88±196.97▪◊	3642.50±223.62
Positive control + concentrated sage infusion	10927.56±2621.34▪◊	147196.25±15123.56▪	33381.56±5966.13▪◊	23065.63±2000.73▪
Positive control + diluted sage infusion	13425.06±2251.64▪	150388.31±13893.05▪	41890.44±13603.81▪◊	25650.63±3013.46▪
Positive control + sage phyto-tea	14465.00±2056.39▪	149916.44±9578.24▪	31495.19±7064.38▪◊	23854.00±2987.85▪

Note: * in relative light units – RLU;
▪ $p < 0.001$ compared to negative control;
◊ $p < 0.001$ compared to positive control

During the explosion with a mutagen 4-NQO, the induction factor of the SOS response of the pColD-*lux* biosensor was 29.94, and when combined with 4-NQO with a concentrated sage extract response was 24.44; with diluted infusion – 30.02; with phyto-tea – 32.35. The induction factor of the pRecA-*lux* biosensor SOS response after exposion to 4-NQO was 8.66, and combination of 4-NQO with a concentrated sage extract – 8.47; with diluted infusion – 8,66; with phyto-tea – 8.63.

Hydrogen peroxide induced luminescence in the pKatG-*lux* biosensor, the induction factor of SOS response was 42.06, and in combination with concentrated sage infusion, this indicator decreased to 23.73; with diluted infusion – to 29.78; with phyto-tea – to 22.39. The induction factor of the pSoxS-*lux* biosensor SOS response was 6.62 after treating with oxidant paraquat, and 6.69 in combination with hydrogen peroxide and concentrated sage infusion; with diluted sage infusion – 7.44; with phyto-tea – 6.92.

According to the presented results, inhibition of the luminescence level after exposion with infusions together with the oxidant was observed in the biosensor pKatG-*lux*. During the combined action of mutagen and infusion on the pColD-*lux* and

pRecA-*lux* biosensors, as well as with the oxidant on the pSoxS-*lux* biosensor, no luminescence was inhibited (table 1). The level of inhibition depended on the type of infusion. Thus, a concentrated infusion and tea of sage showed a strong antioxidant effect against hydrogen peroxide, while the inhibition were 43.6% and 46.8%, respectively. Diluted sage infusion gave a moderate antioxidant effect with an inhibition rate of 29.2%. Concentrated sage infusion statistically significantly reduced the genotoxic effect of 4-NQO, but its inhibitory effect was only 18.4%. This effect is considered as weak, concluded as not positive antioxidant effect. Thus, based on the obtained results, it can be assumed that the composition of the sage extracts contains biologically active substances that can inactivate hydroperoxides and organic peroxides.

Similar studies were related to infusion and phyto-tea of oregano (table 2). Oregano infusions did not show genotoxic and oxidative activity. The induction factor of the SOS response of the pColD-*lux* and pRecA-*lux* biosensors after treatment with concentrated infusion of oregano were 0.93 and 0.95, respectively; diluted – 0.83 and 1.00, and phyto-tea – 1.13 and 1.06. The induction factor of the SOS response of the pKatG-*lux* and pSoxS-*lux* biosensors after treatment with the concentrated infusion of oregano were 1.82 and 1.11, respectively; diluted – 1.49 and 1.08, phyto-tea – 1.17 and 1.12.

Table 2 – Induction of luminescence in bacterial lux-biosensors with biologically active substances of extracts and oregano herbal tea

Experiment variance	Induction of luminescence* in bacterial *lux*-biosensors			
	E.coli MG1655 (pColD-*lux*)	*E. coli* MG1655 (pRecA-*lux*)	*E. coli* MG1655 (pKatG-*lux*)	*E. coli* MG1655 (pSoxS-*lux*)
Negative control	622.94±138.88	16924.94±1285.92	1454.75±258.70	3421.38±772.35
Positive control	19493.44±3804.68▪	158053.75±26241.03▪	38531.87±8069.83▪	25924.88±2233.27▪
Concentrated oregano infusion	580.94±238.83	16083.86±1029.29	2653.69±951.81	3787.80±842.22
Diluted oregano infusion	516.63±129.28	16932.88±1771.86	2171.33±1702.02	3691.31±850.38
Oregano phyto-tea	705.13±349.98	17892.88±2410.38	1697.63±527.44	3820.00±777.98
Positive control + concentrated oregano infusion	16520.27±4659.67▪	152401.19±36735.03▪	29811.63±6138.44▪◊	25216.56±2842.05▪
Positive control + diluted oregano infusion	18461.75±4659.67▪	157496.00±41863.05▪	38179.50±10520.68▪	27104.88±1825.17▪
Positive control + oregano phyto-tea	18330.36±4599.71▪	157377.00±45535.67▪	38380.06±7586.94▪	27663.94±2973.87▪
Note: * in relative light units (RLU); ▪ $p < 0.001$ compared to negative control				

After the influence of mutagen 4-NQO, the induction factor of the SOS response of the pColD-*lux* biosensor was 31.29, while the action of 4-NQO with a concentrated infusion of oregano the induction factor was 26.52; diluted – 29.64, phyto-tea – 29.43. The induction factor of the pRecA-*lux* biosensor SOS response when exposed to 4-NQO was 9.34, while 4-NQO with concentrated oregano infusion gave 9.00; diluted – 9.31; phyto-tea – 9.30. The treatment with peroxide oxidant resulted in the induction factor of the SOS response of the pKatG-*lux* biosensor, reaching 26.49, when hydrogen peroxide with a concentrated infusion of oregano the induction factor was 20.49; diluted infusion – 26,24; phyto-tea – 26.38. The induction factor of the pSoxS-*lux* biosensor SOS response during exposion to oxidant paraquat was 7.58; and under the combined effect of hydrogen peroxide with concentrated infusion of oregano – 7.37; diluted – 7.92; phyto-tea – 8.09.

As can be seen from the presented results, the inhibition of luminescence in lux biosensors induced oregano infusions and the used mutagens and oxidants was insignificant. Although the concentrated infusion of oregano statistically

significantly reduced the effect of hydrogen peroxide, its inhibitory effect was 22.6%. This effect is considered as weak, so it is not concluded as a positive antioxidant effect.

Study of antigenotoxic and antioxidant activity of chamomile (Matricaria chamomilla L.) and yarrow (Achillea millefolium L.) infusions

Similar to the above, studies of the antigenotoxic and antioxidant potentials of chamomile and yarrow infusions were performed. The induction factor of the SOS response after treatment with a concentrated chamomile infusion on the pColD-*lux* biosensor was 0.81; pRecA-*lux* – 1.0; at pKatG-*lux* – 1.04; on pSoxS-*lux* – 0.89 (table 3).

Table 3 – Induction of luminescence in bacterial lux-biosensors with biologically active substances of infusions and chamomile phyto-tea

Experiment variance	Induction of luminescence* in bacterial *lux*-biosensors			
	E.coli MG1655 (pColD-*lux*)	*E. coli* MG1655 (pRecA-*lux*)	*E. coli* MG1655 (pKatG-*lux*)	*E. coli* MG1655 (pSoxS-*lux*)
Negative control	536.63±128.29	17592.88±3065.23	1474.75±139.94	4623.50±411.71
Positive control	38050.00±9672.50▪▪▪	135312.25±13861.39▪▪▪	36943.13±7684.84▪▪▪	31103.69±4459.14▪▪▪
Concentrated chamomile infusion	435.63±96.04▪	18484.25±6114.46	1541.75±282.85	4120.69±373.01▪▪
Diluted chamomile infusion	458.94±99.27	18549.75±3879.92	1776.69±814.47	4240.19±382.11▪
Chamomile phyto-tea	465.50±97.38	18774.44±4030.50	1708.44±528.81	4322.69±373.48▪
Positive control + concentrated chamomile infusion	35063.44±8622.24▪▪▪	140098.44±28259.16▪▪▪	33758.13±6996.07▪▪▪	29787.69±2643.69▪▪▪
Positive control + diluted chamomile infusion	34276.88±12552.51▪▪▪	144072.56±27339.45▪▪▪	40486.44±10667.17▪▪▪	32229.75±8155.00▪▪▪
Positive control + chamomile phyto-tea	37883.06±9143.91▪▪▪	142755.31±6370.88▪▪▪	42711.50±10755.35▪▪▪	32000.19±5674.40▪▪▪
Note: * in relative light units (RLU); ▪ – p <0.05, ▪▪ – p <0.01, ▪▪▪ – p <0.001 compared to negative contro; ◊ – <0.001 compared to positive control				

During the action of diluted chamomile infusion, the induction factor of the SOS response on the pColD-*lux*, pRecA-*lux*, pKatG-*lux* and pSoxS-*lux* biosensors was respectively 0.86; 1.05; 1.20 and 0.92, after exposion to phyto-tea, respectively, 0.86 and 1.07; 1.16 and 0.93. The induction factor for the SOS response of the pColD-*lux* biosensor was 70.91 after treatment with mutagen 4-NQO, while 4-NQO with concentrated chamomile extract make induction factor 65.34; with a diluted infusion – 63.87, phyto-tea – 70.59. The induction factor of the pRecA-*lux* biosensor SOS response when exposed to 4-NHO was 7.69, while 4-NQO with concentrated chamomile infusion, it was 7.96; diluted infusion – 8,19, and phyto-tea – 8,11. The induction factor of the SOS response of the pKatG-*lux* biosensor when exposed to hydrogen peroxide was 25.05, and when combined with hydrogen peroxide with concentrated extract of chamomile, it was 22.89; diluted infusion – 27.45, and phyto-tea – 28.96. The induction factor of the pSoxS-*lux* biosensor SOS response when exposed to paraquat was 6.73, and when combined with hydrogen peroxide with concentrated extract of chamomile, 6.44; diluted infusion – 6.97, and phyto-tea – 6.92.

The results obtained demonstrate that chamomile infusion did not show genotoxic, prooxidant and protective activity in the bioluminescent test (*lux*-biosensors).

Table 4 presents the level of luminescence induced by separate and joint exposure to yarrow infusions of genetically modified *E. coli* strains (*lux*-biosensors) with mutagen and oxidants. The induction factors of the SOS response when the concentrated infusion of the yarrow affects the pColD-*lux*, pRecA-*lux*, pKatG-*lux* and pSoxS-

lux biosensors were respectively 0.82; 0.97; 1.61 and 1.19; after exposure with a diluted infusion – respectively 0.89; 0.96; 1.62 and 1.17; while after treatment with phyto-tea, respectively, 0.90; 0.96; 1.62; 1.12. The detected increase in the luminescence level by yarrow infusions exposure was not statistically significant compared with the negative control.

Table 4 – Induction of luminescence in bacterial biologically active substances of infusions and yarrow phyto-tea

Experiment variance	Induction of luminescence* in bacterial *lux*-biosensors			
	E.coli MG1655 (pColD-*lux*)	*E. coli* MG1655 (pRecA-*lux*)	*E. coli* MG1655 (pKatG-*lux*)	*E. coli* MG1655 (pSoxS-*lux*)
Negative control	768.88±212.53	19069.50±2018.30	1739.13±290.49	5713.25±1407.37
Positive control	12799.75±1888.96▪	150246.56±9357.84▪	52460.81±16101.92▪	54014.69±24676.21▪
Concentrated yarrow infusion	631.19±217.63	18444.56±2619.89	2802.06±922.37▪◊	6793.63±2198.04◊
Diluted yarrow infusion	681.63±177.90	18234.00±2642.78	2822.69±1257.35▪◊	6686.94±1374.93◊
Yarrow phyto-tea	689.25±223.47	18245.44±2919.91	2674.69±1285.53▪◊	6430.31±1229.23◊
Positive control + concentrated yarrow infusion	12437.00±834.38▪	168456.31±35927.55▪	48398.63±11236.80▪	48551.31±16201.76▪
Positive control + diluted yarrow infusion	13208.25±1190.94▪	157940.13±21450.67▪	54520.94±13814.64▪	48607.44±18611.62▪
Positive control + yarrow phyto-tea	13823.00±980.31▪	162980.69±34748.10▪	50745.00±16568.08▪	43915.13±16867.71▪
Note: * in relative light units (RLU); ▪ $p < 0.001$ compared to negative control; ◊ $p < 0.001$ compared with positive control				

The induction factor of the pColD-*lux* biosensor SOS response affected by 4-NQO was 16.65, which statistically significantly exceeds the level of negative control. The combined effect of mutagen 4-NQO with a concentrated, diluted infusions and phyto-tea of yarrow, the induction factors were respectively 16.18; 17.18 and 17.98. On the pRecA-*lux* biosensor, the induction factor of the SOS response, treated with 4-NQO, was 7.88, which is also statistically significantly higher than the negative control level. With the combined effect of the mutagen 4-NQO with a concentrated infusion of yarrow, the induction factor of the SOS response was 8.83; diluted infusion – 8.28, and phyto-tea – 8.55. SOS-response of the pKatG-*lux* biosensor to hydrogen peroxide was 30.16, while in combination with concentrated infusion of yarrow – 27.83; diluted infusion – 30,20 and phyto-tea – 29,18. During the exposure to paraquat, the SOS response of the pSoxS-*lux* biosensor was 9.45, while after treatment with a concentrated infusion of yarrow, it was 8.50; diluted infusion – 8.51 and herbal tea – 7.69. The inhibition of the luminescence level induced by the infusions of yarrow under joint action with the mutagen and oxidants was not shown on the used strains (Table 4).

Discussion

Microbiological tests are short-time demanding methods for assessing the toxic and mutagenic potential of various chemical compounds. Currently, along with the Ames test, bacterial *lux*-biosensors are being widely used. *Lux*-biosensor is a complex of sensory bioluminescent strains that respond by changing the luminescence intensity to toxicants specific for each strain. The bioluminescent test has known not only as a test system for evaluating genotoxicants, but also for evaluating the antioxidant and antigenotoxic activity of biologically active substances [16, 17]

Applying the bioluminescent test, we investigated the genotoxic, oxidative, antigenotoxic and antioxidant properties of infusions of the medicinal plants of sage, oregano, chamomile and yarrow, belonging to the local flora and widely used in traditional medicine. The genotoxic and antigenotoxic activity of infusions was determined

on strains *E. coli* MG1655 (pColD-*lux*) and *E. coli* MG1655 (pRecA-*lux*), and oxidant and antioxidant on strains *E. coli* MG 1655 (pSoxS-*lux*) and *E. coli* MG1655 (pKatG-*lux*).

ColD-biosensor is used for the primary detection of genotoxic agents. In the hybrid plasmid pColD, transcription of the luminescence genes is under the control of the SOS promoter of the *cda* gene. The *cda* gene obtained from the plasmid pColD-CA23, which encodes colicine synthesis, necessary for cells only under stressful conditions, being released into the external environment as a killer [18]. Biosensors with PkatG and PsoxS promoters detect the presence of oxidants, which form hydroperoxide and superoxide anion radical in the cell. A characteristic sign of oxidative stress in *E. coli* is the induction of antioxidant system genes and an increase in the activity of antioxidant enzymes encoded by these genes [19]. The *katG* gene determines catalase synthesis; its promoter PkatG (protein-activator OxyR) specifically reacts to hydrogen peroxide and organic peroxides. The PsoxS promoter (SoxR activator protein) specifically reacts to superoxide anion radicals.

Studies demonstrates that the induction factor for the SOS response of *E. coli* MG1655 (pColD-*lux*) and MG1655 (pRecA-*lux*) when adding infusions of sage, oregano, chamomile and yarrow was significantly lower than the values of this indicator after exposure to 4-NQO ($p < 0.001$). In this bioluminescent test, no genotoxic and oxidative activity was detected in the infusions during the study.

With the combined effect of infusions with toxicants, no statistically significant decrease in the SOS response on the pColD-*lux*, pRecA-*lux* and pSoxS-*lux* sensors induced by 4-NQO and paraquat was observed. However, infusions of sage when combined with hydrogen peroxide statistically significantly reduced the SOS responses on the pKatG-*lux* sensors ($p < 0.001$). The degree of inhibition of the damaging effect of the oxidant depended on the concentration of the infusion. A strong antioxidant effect in the test system used was noted with a concentrated infusion of sage, prepared according to the recipe, and in phyto-tea.

Sage leaves contain essential oils (up to 2%), including camphor, cineole, D-α-pinene, α- and β-thujone, D-borneol; tannins, alkaloids, some acids, sodium, potassium, calcium, vitamins A, C, E, K, fiber, and flavonoids [8, 12, 20, 21]. Oregano grass contains from 0.3 to 1% of essential oil, which consists of phenols (up to 44%), thymol and its isomer carvacrol; bi- and tricyclic sesquiterpenes (12.5%); tannins, ascorbic acid, and flavonoids [8, 11, 22]. Chamomile inflorescences contain essential oil (0.2 – 0.8%), consisting of the main biologically active substances – chamazulene, its precursor prohamazulene and other monoterpenes and sesquiterpenes; flavonoids, derivatives of apigenin, luteolin, quercetin, kaempferol, isorhamnetin; coumarins, sesquiterpene lactones: matricin, matricarin, phytosterols, phenolcarboxylic acids, choline, organic acids (isovaleric, salicylic, caprylic), vitamin C, carotene, gums, mucus, bitterness, polyacetylenes, macro- and microelements [8, 9]. The shoot parts of the yarrow during the flowering period contain flavones, alkaloids, coumarins, aconitic acid, bitter and tannins, resins, organic acids, inulin, asparagine, mineral salts, vitamins C and K, phylloquinone, carotene, choline. Also in the leaves and inflorescences of the yarrow contained with an essential oil (up to 0.85%), which consists of monoterpenoids (cineol (8-10%), camphor, tuyol), sesquiterpenoids – achillin, acetylbalhinolide, karyofillen, azulene, esters, L -Borneol, β-pinene, L-limonene, thujone, bornyl acetate [8, 10, 23].

Depending on the type of extraction and the sensitivity of the method, plant infusions may show varying degrees of biological activity. Kocak M.C. et al. found that the methanol, water, and ethyl acetate extracts of *Salvia cadmica* in different test systems demonstrate different antioxidant activity. The methanol extract showed strong activity on phosphomolybdenum, in the DPPH and CUPRAC method, as well as significant activity in inhibiting L-glucosidase and L-amylase. While the aqueous extract represented strong activity against the chelating effect, in the ABTS and FRAP methods. All extracts did not show activity against AChE, BChE and tyrosinase. At the same time, a strong correlation was seen between the total content of phenolic compounds and the biological activity of the infusions [20].

The composition of medicinal plants includes many natural antioxidants of the phenolic class, which cause their antioxidant, anti-inflammatory, antimicrobial, antispasmodic and neuroprotective actions. Phenolic and polyphenolic compounds are involved in redox reactions and in the neutralization processes of reactive oxygen species. There is an evidence of the presence of antimutagenic and anticarcinogenic activities of polyphenols [24].

Thus, using bioluminescent test, the antioxidant activity of the concentrated infusion and sage phyto-tea using the pKatG-*lux* biosensor is shown. Taking into account investigating medicinal plants contain a lot of BASs, and the test did not reveal antigenotoxic and antioxidant activity, it can be assumed that the

preparation of infusions did not extract the right amount of BAS to detect its activity.

Phyto compounds affect the metabolic processes and neutralization of foreign substances, including carcinogens and mutagens. They have the ability to bind free radicals and reactive metabolites of foreign substances, inhibit enzymes, activating xenobiotics and activate detoxification enzymes [25]. A comprehensive study of phyto compounds as potential protectors in the toxic, genotoxic and mutagenic effects of various environmental pollutants on the body is necessary.

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