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SALVESTROLES AS POWERFUL PLANT ANTI-CANCER ANTIOXIDANTS

*Posted By **Zaure G. Aytasheva**, Thursday, March 19, 2015*
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Communicated by Dr. Galiya Shalakhmetova

Every day we are severely affected by a range of additional chemicals called "*xenobiotics*". Xenobiotics enter into a human body through lungs, skin or a number of food-mediated paths as a part of air pollution, food contaminations, drinks , and *medicines* (M). Some xenobiotics have no any impact on a human body. However, their majority may cause biological responses. Organism responds to M as well as other kinds of xenobiotics. Moreover, the medicines may play through various effecting mechanisms at the level of individual organism. As a rule, it leads to M's neutralization and removal. Some medicines being soluble in the water are then taken up by kidneys in an unchanged form. Other substances may undergo transformation initiated by the enzymes able to alter their chemical nature. Thus, *biotransformation* is considered as general concept covering all chemical changes happening to the xenobiotics in human or animal body. In result of biological transformation xenobiotics are known, on the one hand, to reduce or completely lose their solubility in fats (becoming less liposoluble) or, on the other hand, decrease their watersolubility (becoming less watersoluble). Another outcome is more complex xenobiotics composed of growing number of ingredients, which would also lead to diverted toxic properties of a xenobiotic.

Enzyme chain providing xenobiotic biotransformation includes mechanisms of human or cellular adaptation to exogenous and endogenous toxicants accumulated in course of evolution. One of such mechanisms is referred as *autoinduction*. It assigns growing enzyme activity in metabolizing of a xenobiotic enhanced by the xenobiotic itself. Autoinduction is regarded as adaptive tool developed on the way of evolution for xenobiotics inactivation, including *phytogenesis*.

Specific group of polyphenols termed "*salvestroles*" was identified in 1998, when joint team of the US pharmacologists led by Professor Daniel J. Burke (http://bims.virginia.edu/faculty/daniel-j-burke/) from University of Virginia (UVA), School of Medicine, and the UK medical chemists under supervision of Prof. Gerry Potter from the University De-Monfort in Leicester (UK) (see at: https://www.facebook.com/Salvestrol/posts/316182245148345) combined their efforts. Before Professor Potter could put forward his synthetic drugs for cancer, he had spent more than two decades. As a result Prof. Potter obtained pure plant substances possessing anti-cancer activity. Prof. Burke and Prof. Potter have termed such natural anti-cancer substances "*salvestroles*"

(from Latin verb "*salve*", "*to rescue*").

Salvestroles themselves are not new for science. Their chemical structure was known long ago, as well as related plant sources, for instance the skins of red, green and blue-black grapes. However prior to Burke&Potter's investigations nothing was known about salvestroles pharmacological features. Resveratrol (see also the review posted at http://www.canceractive.com/cancer-active-page-link.aspx?n=1906 or November paper of Masuelli et al. in "Oncotarget", 5(21):10745-62, 2014) was the first identified salvestrole compound isolated from red grape skins. It is synthesized by red grape skins in response to attack of bacteria and moulds.

Other salvestroles were also detected in fruits of different plants. Salvestroles are generally synthesized only by plants. Resveratrol if a classical plant polyphenolic agent. It has been recently shown to potentiate programmed cell death and enhance the effect of curcumin in neck carcinoma cell lines (Masuelli et al.).

Unlike other xenobiotics, salvestroles exhibit their activity only in cancer cells by preventing cell division or killing malignant cells. Upon digestion of plant material xenobiotics get into the blood channel to fall then into all inner cells and parts of the body. Salvestroles are activated by specific enzyme synthesized in cancer cells designated as CYP1B1. This protein is a member of the cytochrome P450 family of enzymes involved in many processes in the body, such as assisting with reactions that break down drugs and produce certain fats (lipids). The CYP1B1 enzyme participates in biochemical reactions in which an oxygen atom is added to other molecules (http://ghr.nlm.nih.gov/gene/CYP1B1). In cancer cells CYP1B1 is overexpressed, and resveratrol is converted by this enzyme into antileukaemic agent piceatannol. Piceatannol is a tyrosine kinase inhibitor differing from resveratrol by extra-aromatic hydroxy group. CYP1B1 catalyses such aromatic hydroxylation. Piceatannol is anticarcinogenic poison promoting apoptosis.

Uniqueness of CYP1B1 is that it is synthesized in large amounts only in cancer cells. The enzyme is veirtually absent in liver cells, whereas in other normal tissues it may appear in a limited range at low levels. That is why salvestroles remain unmodified in normal tissues and have no affect on healthy cells. This has been demonstrated by leading world research groups. At present, salvestroles are being converted *in vitro* by using CYP1B1 enzyme from cancer cell cultures.

Murray and Mac Fadyen group from Robert Gordon University in Aberdeen, UK (http://www.rgu.ac.uk/dmstaff/mcfadyen-morag-ce) are pointing out CYP1B1 role as a biomarker of the tumour phenotype. They have contributed much to evidencing in favour of over-expression of particular CYP1B1 forms in a wide range of malignant tumours of different histological types.

They also showed for the first time CYP1B1 over-expression in tissue of a malignant tumours of connecting tissues, a breast, a bladder, a brain, a thick and small intestine, a gullet, a kidney, a liver, lymph nodes, an ovary, skin, a stomach and a uterus. In healthy tissues of squirrels this enzyme was not indicated. Over-expression of this enzyme was also determined in tumour machineries coming out of metastasis of the primary tumour.

Several therapeutic strategies based on the over-expression of CYP1B1 in tumours are currently being designed by a Mc Fadyen team. The most developed in terms of clinical trials is an anti-CYP1B1 vaccine generated after the discovery of CYP1B1 in tumour cells. Another route is novel therapeutic strategies targeting CYP1B1 at the site of the tumour, implying molecular modelling technology and chemical synthesis and description of novel CYP1B1 selective

ligands.

Cancer researchers state that cancer cell may appear permanently but the majority of such cells is collapsed before transforming into the tumour. This happens due to salvestroles incoming with vegetable food.

Obviously, application of conventional anti-cancer drugs is interfaced by side effects. These reactions caused by the majority of such medicines are explained by their poisonous nature and lacking specificity to malignant or healthy cells. In case of salvestroles, they are activated only in tumour cells, and therefore are harmless to normal cells. Hence, salvestrole application allows to avoid chemotherapy which is found to be rather heavy for patients. According to scientists of DeMontfort University, Leicester, UK, isolated salvestrole drug granules may completely destroy a tumour within 24 hours. Allegedly, such preparation is 10 thousand times more toxic for tumour cells when compared with cells from healthy tissues.

Salvestroles are actively synthesized in plant berries. In Kazakhstan and other Central Asian countries blackcurrant, strawberry, cranberry, pomegranate, red grapes (and specially their stones), apples, cabbages, and pepper may be used as affluent sources for prospective salvestrole chemistry.

Edited by Dr. Zaure Aytasheva

Tags: *autoinduction biotransformation cancer drug resveratrol salvestrole xenobiotics (add +)*