KEFIRAN REDUCES ATHEROSCLEROSIS IN RABBITS FED A HIGH CHOLESTEROL DIET

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**Aim:** Kefiran is an exopolysaccharide produced by Lactobacillus kefiranofaciens, and has been proposed to have many health-promoting properties. We investigated the antiatherogenic effect of kefiran on rabbits fed a high-cholesterol diet. **Methods:** Male New Zealand White rabbits were fed a 0.5% cholesterol diet without (control group, n=7) or with kefiran (kefiran group, n=8) for eight weeks. The aorta was analyzed by histochemistry and atherosclerotic lesions were quantified. Lipids and sugars in serum were measured. Foam cell formation of RAW264.7 by βVLDL derived from both groups of rabbits was also investigated. **Results:** Cholesterol, triglyceride and phospholipids levels of serum and lipoprotein fractions were not significantly different between these groups. Atherosclerotic lesions of the aorta in the kefiran group were statistically lower than those of the control group, with marked differences in the abdominal aorta. T-lymphocytes were not detectable in the aorta of the kefiran group. Cholesterol contents in stools were almost identical in both groups. Cholesterol content in the liver of the kefiran group was statistically lower than in the control group. Galactose content of βVLDL derived from the kefiran group was higher, and the lipid peroxidation level was much lower than in the control group. RAW264.7 macrophages treated with βVLDL from the kefiran group showed a more spherical shape and accumulated statistically lower cholesterol than macrophages treated with βVLDL from the control group. **Conclusion:** Orally derived kefiran is absorbed in the blood. Kefiran prevents the onset and development of atherosclerosis in hypercholesterolemic rabbits by anti-inflammatory and anti-oxidant actions.
EFFECTS OF LIGNANS FROM SESAME SEED ON GENOMIC AND NON-GENOMIC ESTROGEN SIGNALING

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Currently, uses of phytoestrogen-rich natural products as hormone supplement and chemopreventive agents are increasing. In postmenopausal women, production of estrogen from ovary ceases leading to several health impacts such as hot flashes, osteoporosis, fatigue, and impaired cognition. A number of medicinal plants and several foods such as soy products, flax seed, and dried legume are considered to be nutraceutical chemopreventive agents as they contain phytoestrogens. Sesamin and sesamolin are oil soluble lignans from sesame seeds while sesamol is a phenolic compound derived from conversion of sesamolin during the roasting of sesame seed and processing sesame oil. The three compounds from sesame seeds stimulate genomic estrogen signaling as evidenced by induction of estrogen responsive element (ERE)-dependent transcriptional activation of luciferase reporter and induction of estrogen-regulated progesterone receptor (PGR) and pS2 genes. The activation of genomic estrogen signaling by these compounds is mediated via estrogen receptor (ER) as the antiestrogen ICI 182 780 can abolish these effects. Estrogen and its signaling are known to play a crucial role in development and progression of hormone-dependent breast cancer which the cancer cells express ER subtype alpha (ERα +ve) but not hormone-independent breast cancer (ERα -ve). Use of phytoestrogen as chemopreventive agent in hormone-dependent breast cancer is of concern as it may stimulate tumor growth. We demonstrated that sesamin, sesamolin, and sesamol partially inhibited in vitro growth of hormone-dependent T47D human breast cancer cells while sesamol dose-dependently inhibited growth of hormone-independent MDA-MB231 human breast cancer cells. Interestingly, the three sesame seed compounds induced growth of T47D cells when cultured in estrogen-withdrawal (E2W) medium which mimic post-menopausal condition. Additional to the classical genomic ER signaling, the rapid non-genomic membrane ER (mER) and GPR30/EGFR/MAPK signalings are recently found to be involved in regulation of growth and stress response of cells. Sesamol rapidly induced phosphorylation of EGFR and MAPK in E2W condition suggested that in addition to genomic ER it may also activate the rapid non-genomic ER signaling. Taken together, our studies demonstrate that sesamin, sesamolin, and sesamol from sesame seed are phytoestrogens. Their weak estrogenic properties should be of benefit as a hormonal supplement in postmenopausal women. However, precautions should be taken in postmenopausal women with hormone-dependent breast cancer.
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HEALTH BENEFICIAL EFFECTS OF PHYTOPHARMACEUTICALS AND PHYTONUTRIENTS: XENOHORMETIC PERSPECTIVES

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A wide variety of phytochemicals present in our diet, including fruits, vegetables, and spices, have been shown to possess a broad range of health-beneficial properties. The cytoprotective and restorative effects of dietary phytochemicals are likely to result from the modulation of several distinct cellular signal transduction pathways. Phytopharmaceuticals/phytonutrients, either alone or in combination, maintain a precise control over cellular redox status by suppressing activation of various upstream kinases, their downstream transcription factors and their regulators. From an evolutionary perspectives, many dietary phytochemicals that are synthesized as secondary metabolites function as toxins, that is, "phytoalexins," and hence protect the plants against insects and other damaging organisms, microbial infection and stresses. However, at the relatively low doses consumed by humans and other mammals these same “toxic” plant-derived chemicals activate adaptive cellular stress response signal transduction pathways, conferring stress resistance and other health benefits. This phenomenon has been referred to as xenohormesis. One of the key players responsible for the the xenohormesis mechanisms underlying cytoprotective effects of some dietary phytochemicals is the nuclear transcription factor erythroid 2p45 (NF-E2)-related factor 2 (Nrf2) that has been evolutionarily conserved in diverse species.
SAFETY RE-EVALUATION OF CHINESE TRADITIONAL MEDICINE IN INJECTION FORMULATION

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Lianbizhi Injection was developed as a single component of Traditional Chinese Medicine (TCM) injections in 1970s. With the increased clinical applications, the relevant reports of adverse reactions were increased. Therefore, we carried out safety re-evaluation of the Lianbizhi Injection in this program, based on the guiding spirit of the SFDA note for the industry, and on the adverse reactions of Lianbizhi Injections reported in clinicals. Firstly, the general toxicity tests such as acute toxicity test, single dose kidney toxicity test, 30-day repeated dose toxicity test and allergy test had been conducted to explore the toxicity of two kinds of formulations of Lianbizhi Injections (the concentrations of Andrographolidi Natrii Bisulfs for Lianbizhi Injections A and B were 235.5 and 117.4mg/ml, respectively, with relevant impurities contents being 1.3% and 50.9%, respectively). Secondly, the nephrotoxicity mechanisms are explored, by using modern metabonomic technologies, in vitro cytotoxicity test and the combination effect study with of kanamycin. The results of studies in vivo and in vitro confirmed that Lianbizhi Injections had potential nephrotoxicity in high concentration. The mechanism of renal injury induced by Lianbizhi Injections may be related to affecting the osmolality in kidney medulla and interference the activity of related mitochondria enzymes in renal cell, involving in affecting mitochondria energy metabolism, changing the redox state, resulting in excessive ROS, destructing the cell membrane permeability, declining MMP, mitochondrial dysfunction, leading to CytC releasing from mitochondria to trigger apoptosis or necrosis. The toxic effects will occur when Lianbizhi Injections was used in large dose and unreasonable combination therapy. The related substances in the preparation may have great influence on the safety of Lianbizhi Injections.

Keywords: Lianbizhi Injection, Andrographolidi natrii bisulfs, Safety re-evaluation, toxicity, metabonomics