Oxid Antioxid Med Sci 2013; 2(1):1-4 *ISSN: 2146-8389*

GESDAV

Oxidants and Antioxidants in Medical Science

available at www.scopemed.org

Invited Review

Phytoestrogens in gynecology - antioxidative role

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Received February 3, 2013
Accepted March 3, 2013
Published Online March 23, 2013
DOI 10.5455/oams.030313.ir.001

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Key Words
Antioxidants; Menopause; Phytoestrogens

Abstract

It has been shown that higher levels of estrogens in females protect them against aging by up-regulating the expression of antioxidant longevity-related genes. Phytoestrogens are naturally occurring polycyclic phenols found in certain plants that have weak estrogenic effects due to the fact that they are structurally and functionally similar to 17ß-estradiol, and thus, bind to estradiol receptors. Therefore, isoflavones and other phenolic compounds decrease the increased level of markers of oxidative stress and boost DNA resistance to oxidative damage. Consequently, menopausal women who are receiving phytoestrogens have multiple benefits. Synergetic action of estrogenic and antioxidative mechanism of action exerts positive effects on cardiovascular, immunological and central nervous system. Moreover, they can have potential role in prevention and treatment of some cancers. Therefore, it is advised that menopausal women should get phytoestrogen supplementation.

An antioxidant is a molecule that inhibits the oxidation process of other molecules [1]. Although oxidation reactions are crucial for life, they can also be damaging, as during them free radicals can emerge, which can cause damage or death to the cell. Therefore, oxidative stress is an important part of many human diseases. Antioxidants prevent this by being oxidized themselves or by removing free radical intermediates, thus inhibiting other oxidation reactions. Water-soluble antioxidants react with oxidants in the cell cytosol and the blood plasma, while lipid-soluble antioxidants protect cell membranes from lipid peroxidation [2].

These compounds may be synthesized in the body or obtained from the diet. All organisms (plants, animals) have numerous antioxidant metabolites and enzymes that work together to prevent oxidative damage to cellular components. Moreover, many vitamins and minerals have shown antioxidant characteristics [3]. Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer, coronary heart disease, cognitive functioning, neurological diseases and even altitude sickness. The most famous antioxidants are vitamins C and E, carotenoids (found in fresh fruits and vegetables) and polyphenolic antioxidants like resveratrol and isoflavones (found in different plants such as soy, red clover, tea, coffee, chocolate, cinnamon, oregano) [4]. Dietary total antioxidant capacity, based on the cumulative antioxidant activities of all the antioxidants present in food, has been shown to be inversely correlated with risks of different chronic diseases [5].

Phytoestrogens are naturally occurring polycyclic phenols found in certain plants that may, when ingested and metabolized, have weak estrogenic effects due to the fact that they are structurally and functionally similar to 17ß-estradiol and therefore bind to estradiol receptors (mainly to estradiol $ß_2$ receptors) [6-9].

The most important groups of phytoestrogens are isoflavones (formononetin, resveratrol, biochanin A, daidzein, genistein, quercetin, O-desmethylangolensin-ODMA, equol, *etc*). Daidzein and genistein represent phytoestrogens that are most commonly used as food supplements and also the most thoroughly investigated [6-9]. They are the main isoflavones extracted from soy, the plant popular in human food. Apart from soy,

several other plants contain isoflavones, such as legumes, red clovers, black cohosh, dong quai, kudzu root, lentils, kidney beans, lima beans, broad beans, Panax ginseng, licorice, wild Mexican yam, bran, cereal, chickpeas, bluegrass, some sorts of fruits like citruses and vegetables [6].

Isoflavones and other phenolic compounds decrease the increased level of markers of oxidative stress (red blood cell membrane fluidity, activity of the red blood cell cytosolic enzyme OGA and lymphocyte DNA susceptibility to oxidative stress) and boost DNA resistance to oxidative damage [10]. Isoflavones are well-known not only as antioxidants, but also as chemo-preventive and anti-inflammatory agents that can modulate apoptosis [11]. They could be involved in regulation of the immune response and in that way reduce prevalence of chronic health disorders of their regular consumers [12].

Researchers have found that mitochondrial oxidative stress is higher in males than females and that the higher levels of estrogens in females protect them against aging by up-regulating the expression of antioxidant longevity-related genes. The chemical structure of estradiol confers antioxidant properties to the molecule. Data show that physiological concentrations of estrogens activate estrogen receptors and the mitogen-activated protein kinase (MAPK) and nuclear factor kappaB (NFκB) pathway [13]. Activation of NFκB by estrogens subsequently activates the expression of antioxidant enzymes manganese superoxide dismutase (Mn-SOD) and glutathione peroxidase (GSH-Px). Furthermore, it was demonstrated that genistein, the most abundant phytoestrogen in soya, exerts the antioxidant effect of estradiol at nutritionally relevant concentrations by the same mechanism. Estrogens and phytoestrogens up-regulate expression of antioxidant enzymes via the estrogen receptor and MAPK activation, which in turn activate the NFκB signaling pathway, resulting in the up-regulation of the expression of longevity-related genes [13]. Consequently, women who are treated with phytoestrogens in menopause have a benefit, apart from estrogenic, also from the antioxidative effects of administered substances. Dietary polyphenols modulate plasma non-enzymatic antioxidant capacity (NEAC) by scavenging free radicals and modifying cellular redox transcription factors [14].

Numerous antiproliferative properties are suggested for phytoestrogens contrary to estrogen effects. This is due to diverse activities of the estrogen receptors and the higher affinity of phytoestrogens for ER-ß than ER-α [9]. The effects of phytoestrogens on cell growth and proliferation may be explained by their ability to alter the expression of a number of proteins that control cell cycle and induce cell cycle arrest and apoptosis. Genistein inhibits tyrosine protein kinases, which plays a key role in tumor genesis. It also inhibits deoxyribonucleic acid (DNA) topoisomerases I and II, and may prevent cell mutations by stabilizing cell DNA [6]. As an antioxidant genistein inhibits formation of tumor promoter-induced hydrogen peroxide and superoxide anion in cultured human cells. Daidzein appears to have similar antioxidant activities. Genistein also induces apoptosis; inhibits angiogenesis, subsequent tumor growth, and cell differentiation; and may reduce malignant cell metastasis as a result [6, 11]. On the other hand, estrogen receptor (ER) negative cells may have different responses to phytoestrogen exposure. In the ER negative breast cancer cell line, resveratrol inhibited cell proliferation at all concentrations lower than 10 nM. Similarly, low concentrations of quercetin and genistein reduced proliferation or had no stimulatory effect on ER negative MDA-MB-231, HCC-38, and HeLa cells lines of breast and cervical cancers [6, 14].

Literature data suggest a potential role for phytoestrogens and other antioxidants as adjuvants in cancer therapy. Studies have shown that a high intake of anti-oxidant-rich foods is inversely related to cancer risk because antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread [15]. Diverse dietary constituents such as vitamins A and D, isoflavones (especially genistein), epigallocatechin gallate (EGCG), sulfora-phane, curcumin, piperine, theanine and choline have been shown to modify self-renewal properties of cancer stem cells [16]. Phytoestrogens suppressed mammary carcinogenesis, reduced tumor incidence, and increased tumor latency [6]. The molecular mechanisms of action through which phytoestrogens prevent tumor induction may be by exerting their antiproliferative activity. They are found to inhibit the proliferation of MCF-7/Vec and MCF-7 HER2 cells lines of breast cancer. This growth inhibition was accompanied with an increase of sub-G(0)/G(1) apoptotic fractions. Genistein and quercetin induce extrinsic apoptosis pathway, by up-regulating p53. Genistein and quercetin reduce the phosphory-lation level of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; the inhibitor of NFkB), and abrogate the nuclear translocation of p65 and its phosphorylation within the nucleus [17]. Moreover, equol, daidzein and genistein may have significant antiinvasion effect in DU145 cell lines of prostate cancer. The effects induced by equol may relate to its antioxidant effect mediated by phosphatase and tensin homologue (PTEN) deleted on chromosome ten. Matrix metalloproteinase-2, matrix metalloproteinase-9, and urokinase type plasminogen activator, the crucial members in metastasis of prostate cancer are also down-regulated in patients using

 DOI 10.5455/oams.030313.ir.001

phytoestrogens [18]. Therefore, phytoestrogens might be used for additional or alternative therapy for pancreatic, prostate and breast cancers as well as some types of bladder, laryngeal and myelogenous leukemia [19, 20]. Additionally, antioxidants are believed to protect from the damage inflicted by radiation therapy in normal tissues [21]. The effects of isoflavones and other antioxidants on gynecological cancers are yet to be additionally precised.

Antioxidant foods as dietary components play an important role in the management of cardio-metabolic disorders [22]. Supplementation with dietary antioxidants has been shown to lower blood pressure and plasma inflammatory cytokines and vascular inflammation in patients with essential hypertension [23]. There is documented evidence of disease-modifying effects of nutritional compounds with anti-inflammatory and antioxidant effects such as phytoestrogens. It was recently proven that phytoestrogens exert positive effects on lipid profile of menopausal women. Polyphenolic compounds (flavonoids, isoflavones, phenolic acids and lignans) increase plasma antioxidant capacity, decreased oxidative stress markers as well as total and LDL cholesterol [6-9]. They play an important therapeutic role in attenuating oxidative damage induced by metabolic syndrome associated with atherogenic dyslipidemia and a pro-inflammatory, pro-thrombotic state, at a sub-cellular level [24]. Genistein stimulates nitric oxide production and thus might lower blood pressure [25]. Genistein prevents any isoproterenol-induced increase in heart weight to body weight ratio, left ventricular mass (echocardiographic), myocardial 1-OH proline, fibrosis, myocyte size and myocardial oxidative stress. On the other hand, these beneficial effects of genistein can be blocked by nonselective nitric oxide synthase (NOS) inhibitors (L-NAME), but not by selective iNOS inhibitors (aminoguanidine) [26]. These findings suggest a nutritional approach of using a soy-based diet for the prevention of oxidative-stress-related diseases such as heart failure and hypertension [27, 28].

Phytoestrogens are also found to have neuroprotective and myorelaxant effects similar to estrogens [29]. Phytoestrogens have been suggested to have the potential to prevent Alzheimer's disease because of their anti-amyloidogenic, anti-oxidative, and anti-inflammatory properties. These polyphenolic phytochemicals also activate adaptive cellular stress responses, called 'neurohormesis', and suppress disease processes [30]. Higher dietary intake of antioxidant vitamin E, but not vitamin C, beta carotene, or flavonoids, was associated with a decreased long-term risk of dementia [31]. Literature data regarding the effects of soy and soy isoflavones on cognitive function suggests some benefit for soy on cognitive function in women younger than age 65 with little benefit for women over age 65. These findings support a critical window hypothesis that younger postmenopausal women treated close to the final menstrual period will have more cognitive benefit from phytoestrogen supplementation than older women treated many years after the final menstrual period [32].

In conclusion, it can be said that menopausal women who are receiving phytoestrogens have multiple benefits. Besides binding to ER-ß2 phytoestrogens also have anti-oxidative effects and synergetic action of these two mechanisms exerts positive effects on cardiovascular, immunological and central nervous system. Moreover, they can have potential role in prevention and treatment of some cancers. Therefore, it is advised that menopausal women should get phytoestrogen supplementation.

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