Green Reports

Ariviyal Publishing

Review Article

DOI: 10.36686/Ariviyal.GR.2022.03.08.041

Green Rep., 2022, 3(8), 19-23.

Concerns about Phytoestrogens and Soy Cultivation: An Update

Sergei V. Jargin

Department of Pathology, Peoples' Friendship University of Russia, Moscow.

Corresponding author E-mail address: sjargin@mail.ru

ISSN: 2582-6239

Crossref

Publication details
Received: 09th April 2022
Revised: 26th April 2022
Accepted: 26th April 2022
Published: 10th May 2022

Abstract: Phytoestrogens are present in different edible plants being most abundant in soy; among others, they are used to compensate for estrogen deficiency in menopause. The estrogenic potential does not prevent from the use of soy in infant foods and other foodstuffs. Supposed benefits, if even observed in Asian populations, should not be automatically extrapolated onto Europeans and other peoples having no historic adaptation to soy. Derangements of the reproductive health and feminizing effects may be statistically significant in large populations. This matter should be clarified by independent research, which can have implications for the future of soy in the agriculture.

Keywords: Phytoestrogens; Soy Beans; Isoflavons; Feminization

1. Introduction

Phytoestrogens (PhE) are plant-derived substances having structural similarity with estradiol.[1,2] The most extensively studied PhE are isoflavones and coumestans. Isoflavones are abundant in soy. Some other plants also contain PhE, in particular, red clover. The consumption of PhE and soy foods has been associated with health benefits; however, adverse effects on the reproductive and endocrine system seem to be undervalued.[1] Some epidemiological studies suggest that dietary intake of PhE contributes to a decreased incidence of postmenopausal cardiovascular and thromboembolic events.[3] In the same review, it was acknowledged that trials on PhE had been limited in many aspects including the number of participants enrolled, clinical endpoints studied, and lack of long-term follow-up.[3] According to a Cochrane review, there is no conclusive evidence that PhE reduce the frequency or severity of hot flushes and night sweats in peri- and postmenopausal women, while many of the trials were small, of short duration and questionable quality. Moreover, publication bias favored papers with positive results.[4] The analysis of earlier findings from enrichment of diets with soy protein failed to confirm cardiovascular benefits.[5] There is also little evidence in favor of the prevention of menopausal osteoporosis.[2,6-9] Admittedly, the matter is controversial and positive effects of PhE have been reported.[10,11] For example, the following statement appears questionable: "Comparative assessment showed no significant differences between the effectiveness of the hormone therapy and the PhE used in the study, in terms of effects on bone mineral density and bone resorption."[11] The hormonal activity of PhE is known to be much lower than that of estradiol and NETA (norethisterone acetate) used in the same study.[11] The data about safety are conflicting. There have been reports on adverse effects and interactions with other medications.[12,13] Soy is one of the most allergenic foods, so that some people must avoid it.[2,14] The conventional menopausal hormone therapy remains the only treatment that is consistently more effective than placebo in controlled trials.[15] Many high-quality studies on PhE demonstrated no clear benefit and/or potential harm. Obviously, more independent research is needed to formulate recommendations.

The theoretical basis for the use of PhE in the menopause appears doubtful. Biological effects of estrogens are mediated by receptors. It is hard to conceive, why accidental plant-derived analogs must be used instead of natural or synthetic hormones that are complementary to the receptors. Some commercial PhE preparations are mixtures of ingredients of obscure origin having unpredictable effects.[16] Mixed preparations containing both phytoestrogens and estrogens might inhibit the desirable effect by competing for the receptor binding sites, which would possibly increase the required dose. The notion about PhE as a natural and safe alternative to estrogens[17] is unfounded: these substances are in fact less natural for humans than hormones. Moreover, the use of soy as animal fodder can result in the accumulation of PhE and their

derivative equol in meat and other animal products. Equol has an estrogenic potential, it is produced by intestinal bacteria in farm animals and fowl.[18,19] There might be genetic differences in this regard, as human equol producers seem to display a more positive response to isoflavone.[20] Differences have been reported in the prevalence of the equol-producer phenotype between different races, with a higher prevalence among soy-consuming Asian populations.[21] It is probably related to a genetic adaptation of East Asians to soy. Supposed benefits, if even observed in Asians, should not be automatically extrapolated onto Europeans and other peoples having no historic contact with soy. Many studies, mainly from East Asia, tend to positively characterize PhE, reporting risk reduction of cardiovascular disease, of thromboembolic complications, fractures and hot flashes.[22-25] The quality of studies is uneven; the evidence is regarded to be generally weak.[2,26-29] Comparisons were made between residents of different countries and continents or between meat-eaters and vegetarians, assuming that the latter consume more soy.[29] Informativity of such studies is limited due to known and unknown confounding factors. Some reviews concluded that the effectiveness of PhE compared with placebo against hot flashes, vascular and other manifestations of climacteric syndrome and menopause failed the test of randomized clinical trials.[17,26,27,30-34] The beneficial effect of soy proteins on the cardiovascular system and blood lipid profile has not been satisfactorily confirmed.[5,35] In contrast to East Asia, epidemiological studies in Western countries did not reveal a reduction in cardiovascular risks under the influence of isoflavones and lignans (admittedly, a positive effect of high doses of lignans among smokers was noticed). The clinical efficacy of PhE for prevention of cardiovascular diseases is considered unproven.[2] A similar opinion has been expressed in relation to osteoporosis,[2,7,8,9,36,37] although the literature data are diverse.[10,11,38] According to the European Food Safety Authority, existing evidence does not suffice to confirm a relationship between the maintenance of bone mineral density and consumption of soy isoflavones.[2] The use of PhE is not advocated also because of conflicting data about safety.[12] There have been reports on adverse effects and interactions with other medications.[1,2,13,39,40]

Adverse effects of soy products have been reviewed.[1,23,41,42] Derangements of the reproductive health and feminizing effects in men are regarded to be rare and mild[23] but may be statistically significant in large populations. It was reported on dysmenorrhea in adults, change of gender-related behaviors of girls, gynecomastia and erectile dysfunctions in men consuming large quantities of soy products.[1,43-45] A cross-sectional study of 11,688 women showed that abundant intake of isoflavones was associated with an increased risk of lifetime nulliparity and nulligravidity.[46] Hormonal effects of PhE may lead to fertility derangements possibly due to an impact on the menstrual cycle, oocyte quality and endometrial receptivity.[41] An association between soy exposure and early menarche was reported.[47] Experimental data demonstrate that soy isoflavones, also at doses and concentrations observable in humans including infants, can influence neuroendocrine pathways in animals of both sexes. Relevant doses of PhE have an impact on the differentiation of ovaries and fertility e.g. “clover disease” of sheep and similar conditions in cows.[1,22,48-53] Alterations and deficit of male sexual development/behavior were observed in rats and rabbits.[54,55] The reproductive function in animals restored after discontinuation of the PhE-containing feeding.[49,51] The antiandrogenic effect of PhE in patients with prostate cancer has been observed.[40] Moreover, some PhE such as genistein can exert androgenic effects,[56] which is not surprising as PhE are plant substances with accidental similarity to human hormones, so that their effects are unpredictable. It was suggested that PhE are estrogen receptor modulators thus being different from estrogens.[57] The words “modulation” and “regulation” are sometimes used to make impression that certain substances have beneficial effects. However, regulation presupposes a feedback mechanism and cannot be ascribed to a sole substance. Anyway, it is questionable whether a modulation by PhE, also referred to as endocrine disruption,[1,58] is favorable for all soy consumers, especially at a young age. The perinatal period, childhood and puberty are critical periods when maturing systems are particularly sensitive to hormonal disruptions.[58] If even “available knowledge suggests that phytoestrogens can affect a number of physiological and pathological processes related to reproduction, bone remodeling, skin, cardiovascular, nervous, immune systems and metabolism” it is still not a matter-of-course that “due to these effects, phytoestrogens and phytoestrogen-containing diet can be useful for the prevention and treatment of menopausal symptoms, skin aging, osteoporosis, cancer, cardiovascular, neurodegenerative, immune and metabolic diseases”.[59] Clinically relevant effects should be proven according to the principles of evidence-based medicine. The supposition that substances of plant origin are natural for humans is unfounded: it is known that many botanicals are toxic. As the global soy consumption increases, greater awareness of its endocrine-disrupting properties is needed. Parents should be aware of possible estrogenic effects if they choose to feed their infants with soy-based formulas.[1] Finally, soy-containing emulsions are known to provoke cholestasis during pediatric parenteral nutrition.[60]

Another contradiction was encountered in the literature: “Findings from a recently published metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy influences total or free testosterone levels. Similarly, there is essentially no evidence from the nine identified clinical studies that isoflavone exposure affects circulating estrogen levels in men”.[61] In a case report on gynecomastia associated with soy consumption by a man it was noted: “After he discontinued drinking soy milk … his estradiol concentration slowly returned to normal”.[44] Statements of this kind e.g. that there was “no conclusive interaction between soy or isoflavone intake and free testosterone concentrations” or “a systematic review of the literature showed that effect of soy on sex hormones in pre- and post-menopausal women had very small”[23] may be confounding because PhE, being estrogen analogs, exert hormonal effects on their own, not necessarily influencing concentrations of endogenous hormones.

All said, numerous studies positively characterizing PhE cannot be overlooked, although objectivity sometimes appears questionable. It is increasingly difficult these days to distinguish between reliable and unreliable publications. The main purpose of this review was to convey the following notions: (1) PhE are used for compensation of estrogen deficiency in menopause; however, their estrogenic potential does not prevent from the use of soy in infant formulas and other foodstuffs. Note that consumers are sometimes

unable to find out whether a product contains soy. In Russia, a foodstuff with the same label can change its quality and composition. The soy protein is widely used by the food industry, added to meat and other products, often without corresponding information on the labels.[35] As mentioned above, the feminizing effect of soy products may be subtle, detectable only statistically in large populations. This matter should be clarified by independent research. (2) Placebos are often marketed in the guise of evidence-based medications, reviewed previously.[62] For example, the supposed anti-atherogenic action of certain flavonoids including those having estrogenic potential (genistein, quercetin, grape seeds, hop cones etc.) was corroborated by experiments with cell cultures, where the reported accumulation of cholesterol in cultured cells incubated with a serum was interpreted as an indicator of the serum atherogenicity.[63-69] The reliability of these experiments has been questioned; however, the publication series has been continued without references to the published criticism.[70-72] The cell cultures were used for assessment of pro- or antiatherogenic effects of different substances. Of note, some of the "cultures" did not grow; therefore, it might be more appropriate to name these cells, surviving for about 7 days in serum-containing media, not cell cultures but incubated cells.[71] Certain results by the same researchers such as anti-atherogenic effects of mushroom extracts, canned fish or pine needles,[65-67] are doubtful. Recommendations for practice,[68] based on the cell culture experiments discussed above, appear to be unsubstantiated at least in part. Following their concept, the same scientists applied blood apheresis through a column with immobilized LDL to remove "non-lipid atherogenicity factors".[64] The studied patients with angina pectoris had normal blood level of cholesterol. The patients were reported to feel better and endure higher physical loads,[64] which could have been caused by a placebo effect. It is known that invasive procedures can exert placebo effects. Apheresis is usually aimed at removal of excessive lipoproteins, for example, in drug-resistant LDL-hypercholesterolemia or premature atherosclerosis.[73,74] Furthermore, in some Russian-language literature, PhE are promoted by misquoting of foreign literature.[70] For example, in the original: "These compounds seem to be cancer protective… With regard to prostate and colon cancer… epidemiological data related to PhE are still very limited"[75] and in another cited source: "Evidence is beginning to accrue that they may begin to offer protection against a wide range of human conditions, including breast, bowel, prostate and other cancers".[76] In a paper with references to the above articles it is written: "It has been proven that isoflavones can prevent breast, prostate and colon cancer".[77] The statement: "Consumption of soy products... has been associated with reduction of malignancies".[78] It was written with a reference to an irrelevant publication.[79] It was generalized without references that PhE have antineoplastic, antimicrobial and anti-inflammatory properties.[80] Scientifically questionable methods and theories are sometimes used for promotion of drugs, dietary supplements and treatment methods, for the official registration and patenting of drugs, dietary supplements and treatment methods.[62] As a result, substances with unproven effects are recommended or prescribed to patients, who may be misinformed not only by the advertising but also by some publications supposed to be scientific. Research quality and possible conflicts of interest should be taken into account defining inclusion criteria for studies into meta-analyses and reviews.

2. Conclusion

PhE are present in different edible plants being most abundant in soy; among others, they are used to compensate for estrogen deficiency during menopause. However, the estrogenic potential of PhE does not prevent from the use of soy in infant food and other foodstuffs as well as pediatric parenteral nutrition. Feminizing effect of PhE and soy products may be subtle, having potential repercussions for large populations; it can be of particular importance for children and adolescents. This matter should be clarified by independent research, which can have implications for the future of soy in the agriculture.[81]

Conflicts of Interest

The authors declare no conflict of interest.

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