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Soy phytoestrogens: hormonal activity and impact on the reproductive system

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Abstract. *Phytoestrogens (PhE) are contained in soy and some other plants; they are structurally similar to estrogens. PhE are used for substitution therapy in the menopause. However, some recent reviews concluded that no satisfactory evidence has been provided in favor of PhE efficiency against menopausal symptoms compared to placebo. Soy is used as an ingredient of infant food and other foodstuff as well as cattle fodder, so that residual PhE and their degradation products, e.g. equol, having estrogenic activity, can remain in meats. Soy protein is used in the food industry. Disorders of the reproductive system in humans under the influence of PhE are regarded to be rare and mild. There were single reports on altered gender-related behavior in children and feminization associated with soy consumption. In animals, the excessive PhE intake leads to derangements of fertility, sexual development and behavior. PhE are called modulators or disruptors of the endocrine system. There are no reasons to assume that benefits from such modulation would prevail in all soy consumers. Feminizing effects may be inconspicuous but statistically detectable in large populations.*

Keywords: *phytoestrogens; soy; menopause; reproductive system*

Phytoestrogens (PhE) are plant-derived substances with structural similarity to estradiol, although their hormonal activity is much weaker than that of natural and synthetic estrogens. The most extensively studied PhE are isoflavones that are abundant in soybeans [1–3]. Soy protein is used in the food industry; it is added to meat and other products, sometimes without corresponding information on labels [4]. The consumption of PhE and soy foods is associated with health benefits; however, their impact on the reproductive and endocrine system may be underestimated.

Many studies reporting benefits from the intake of soy originate from Eastern Asia [3, 5–7]. The quality of studies is uneven; the evidence is regarded to be weak [2, 8–11]. It can be reasonably assumed that some Asian populations are genetically adapted to soy. On the contrary to East Asian studies, epidemiological research from the West does not generally report a decrease in cardiovascular risks after PhE treatment [2].

One epidemiological study suggested that the dietary intake of PhE contributes to a decreased frequency of postmenopausal cardiovascular and thromboembolic events [12]. In the same review, it was acknowledged that trials on PhE had been limited in many respects including the number of participants,

clinical endpoints studied, and lack of long-term follow-up [12]. PhE were reported to be significantly more effective than placebo in reducing the frequency and severity of hot flashes [7]. However, several reviews concluded that the efficiency of PhE compared to placebo remains unproven [13–17].

Improvements of subjective symptoms must be caused by the placebo effect, at least in part. The evidence from observational studies and randomized trials generally lacked [8, 9]. According to several reviews, there are no reliable arguments in favor of PhE efficiency against menopausal symptoms, and current evidence does not support their use [13–15, 18]. The effectiveness of PhE against vasomotor symptoms failed the test of randomized clinical trials being similar to that of placebo [15, 19].

According to the Cochrane review, there is no conclusive evidence that PhE can reduce the frequency or severity of hot flashes and night sweats in peri- and postmenopausal women, while many of the trials were small, of short duration and questionable quality. Moreover, the publication bias with a preference of papers reporting positive results is a well-known phenomenon [20]. In sum, a definite conclusion on possible health effects of PhE could not be made so far [2].

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The analysis of earlier findings from enrichment of the diet with soy protein has failed to confirm beneficial cardiovascular effects by way of lipid reduction, vasodilatation or lipoprotein oxidation [21]. In particular, there is little evidence in favor of the prevention of menopausal osteoporosis [2, 22–25]. Admittedly, the matter is controversial while positive effects of PhE have been reported [26, 27]. For example, the following statement appears questionable: “Comparative assessment showed no significant differences between the effectiveness of hormone therapy and the PhE used in the study, in terms of effects on bone mineral density and bone resorption” [27] because the hormonal activity of PhE must be much lower than that of estradiol and norethisterone acetate used in this study [27].

According to the European Food Safety Authority, existing evidence does not suffice to establish 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 [28]. There have been reports on adverse effects and interactions with other medications [29]. Moreover, soy is one of the most allergenic foods, so that some people must avoid it [2, 30]. The majority of high-quality studies demonstrated no clear benefit and some potential for harm; therefore, further research is deemed necessary to formulate recommendations. The conventional menopausal hormone therapy remains the only treatment that is consistently more effective than placebo in controlled trials [31].

The rationale for the use of PhE in the menopause is hardly comprehensible. Biological effects of estrogens are mediated by receptors. It remains unclear, why accidental plant-derived analogs should be used instead of natural or synthetic hormones. Some PhE preparations contain a mixture of ingredients of unknown origin that may have unpredictable effects depending on their composition and a patient’s condition; such drugs are difficult to dose [32]. The notion that PhE are a natural and safe alternative to estrogens [15] is unfounded: these substances are in fact less natural for humans than endogenous hormones. Moreover, the use of soy as animal fodder can result in the accumulation of PhE and their active metabolites such as equol in meats and other animal products. Equol has a relatively high estrogenic potential, it is produced by intestinal bacteria in farm animals and fowl [33, 34].

Adverse effects associated with the intake of soy have been reviewed [1, 35–37]. Derangements of the reproductive health and feminizing effects in men are regarded to be rare and mild [35] but may be statistically detectable in large populations. It was reported on dysmenorrhea, slight changes in gender roles in girls and gynecomastia in a man consuming soy product [1, 38, 39].

A cross-sectional study of 11,688 women showed that abundant intake of soy was associated with an increased risk of lifetime nulliparity and nulligravidity [40]. Hormonal effects of PhE may lead to fertility derangements possibly due to an impact on the menstrual cycle, ovum quality and endometrial receptivity [36]. An association between soy intake and early menarche was reported [41].

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 PhE doses have an impact on the differentiation of ovaries and fertility in domestic and other animals [1, 42–46]. Alterations of male sexual development and gender-related behavior were noticed in rats and rabbits, while derangements of the reproductive system were found not only in female but also in male animals [47, 48]. Moreover, some PhE, e.g. genistein, exerted androgenic effects [49], which is not surprising because PhE are botanicals with accidental similarity to human hormones, so that their effects are a priori unpredictable.

It was suggested that PhE are hormone receptor modulators thus being different from estrogens [50]. It is questionable, however, whether such modulation, also called endocrine disruption [1, 51], is favorable for all soy consumers, especially at a young age. The perinatal period, infancy, childhood and puberty are critical periods when the maturing endocrine and reproductive systems are especially sensitive [51]. As soy consumption is increasing worldwide, more consideration of its endocrine-disrupting properties is needed. As mentioned above, a cross-reactivity of PhE with various drugs is possible [1, 2, 28, 35, 36]. Parents should be aware of potential estrogenic effects if they feed their infants with soy-containing baby food [1]. Finally, soy-based emulsions are known as causative factors of cholestasis associated with the pediatric parenteral nutrition [52].

Furthermore, a contradiction can be observed in the literature: it was stipulated that “...findings from a recently published metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy affect 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” [53]. In a case report on gynecomastia associated with soy consumption it was mentioned: “After he discontinued drinking soy milk... his estradiol concentration slowly returned to normal” [39]. Statements of this kind are potentially confusing because PhE, being estrogen analogs, exert hormonal effects on their own, without a direct impact on concentrations of endogenous hormones.

This article was not intended to be a review on PhE: there have been several reviews that are cited here. The main purpose was to convey the following ideas. Firstly, PhE are used for compensation of estrogen deficiency in menopause; however, their hormonal activity does not prevent from the use of soy in infant formulas and other foodstuffs. The feminizing effect of soy products may be subtle, detectable only statistically in large populations. This matter should be further clarified by unbiased research. Secondly, there is a tendency of placebo marketing in the guise of evidence-based medications. The published criticism is sometimes disregarded. For example, a supposed anti-atherogenic activity of certain PhE was corroborated by experiments with cell cultures. The ability of serum to induce accumulation of cholesterol in cultured cells was interpreted as an indicator of, for example, atherogenicity [54, 55].

The results and conclusions of these experiments have been questioned; however, the publication series has been continued without references to comments [56, 57]. PhE were sometimes promoted by means of misquoting [56]. For example, in the original: “These compounds seem to be cancer protective... With regard to prostate and colon cancer...

the epidemiological data related to phytoestrogens are still very limited” [58] 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” [59]. In the article with references to the above publications it is written (from Russian): “It has been proven that isoflavones can prevent breast, prostate and colon cancer” [60]. The statement: “Consumption of soy products... has been associated with reduction of malignancies” [61] was given with a reference to a publication on another topic [62]. In a monograph, it was generalized without references that PhE, for instance, have anti-neoplastic, antimicrobial and anti-inflammatory properties [63]. Scientifically questionable methods and theories are sometimes used for promotion of drugs, dietary supplements and treatment methods [64–66]. As a result, substances with unproven effects are sometimes prescribed to patients.

Conflicts of interests. The author declares the absence of any conflicts of interests and his own financial interest that might be construed to influence the results or interpretation of the manuscript.

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**Фітоестрогени сої:
гормональна активність і вплив
на репродуктивну систему**

Резюме. Фітоестрогени (ФЕ) містяться в сої і деяких інших рослинах; за молекулярною структурою вони подібні до естрогенів. ФЕ використовуються для замісної терапії в період менопаузи. Однак у низці недавніх оглядів був зроблений висновок про відсутність переконливих доказів ефективності ФЕ щодо симптомів клімаксу і менопаузи порівняно з плацебо. Соя використовується як інгредієнт багатьох харчових продуктів, дитячого харчування і кормів для тварин. ФЕ та їх гормонально активні метаболіти (еквол) можуть зберігатися в м'ясних продуктах. Соевий білок використовується в харчовій промисловості. Порушення функцій репродуктивної системи людини під дією

ФЕ вважаються нечастими і слабовираженими. Описані поодинокі випадки фемінізації, а також зміни гендерної поведінки в дітей при підвищеному споживанні сої. У тварин багаті на ФЕ корми викликають порушення фертильності, статевого розвитку і поведінки. ФЕ називають модуляторами або дизрапторами ендокринної системи. Проте немає підстав припускати, що модуляція корисна для всіх споживачів соєвих продуктів. Фемінізуючі ефекти можуть бути непомітними, проявляючись статистично у великих популяціях.

Ключові слова: фітоестрогени; соя; менопауза; репродуктивна система

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**Фитоэстрогены сои:
гормональная активность и воздействие
на репродуктивную систему**

Резюме. Фитоэстрогены (ФЭ) содержатся в сое и некоторых других растениях; по молекулярной структуре они сходны с эстрогенами. ФЭ используются для заместительной терапии в период менопаузы. Однако в ряде недавних обзоров был сделан вывод об отсутствии убедительных доказательств эффективности ФЭ в отношении симптомов климакса и менопаузы по сравнению с плацебо. Соя используется как ингредиент многих пищевых продуктов, детского питания и кормов для животных. ФЭ и их гормонально-активные метаболиты (эквол) могут сохраняться в мясных продуктах. Соевый белок используется в пищевой промышленности. Нарушения функций репродуктивной системы человека под действием

ФЭ считаются редкими и слабовыраженными. Описаны единичные случаи феминизации, а также изменения гендерного поведения у детей при обильном потреблении сои. У животных богатые ФЭ корма вызывают нарушения фертильности, полового развития и поведения. ФЭ называют модуляторами или дизрапторами эндокринной системы. Однако нет оснований предполагать, что модуляция полезна для всех потребителей соевых продуктов. Феминизирующие эффекты могут быть незаметными, проявляясь статистически в больших популяциях.

Ключевые слова: фитоэстрогены; соя; менопауза; репродуктивная система