Soy and phytoestrogens: possible side effects

Soja und Phytoöstrogene: mögliche Nebenwirkungen

Abstract

Phytoestrogens are present in certain edible plants being most abundant in soy; they are structurally and functionally analogous to the estrogens. Phytoestrogens have been applied for compensation of hormone deficiency in the menopause. At the same time, soy products are used in infant food and other foodstuffs. Furthermore, soy is applied as animal fodder, so that residual phytoestrogens and their active metabolites such as equol can remain in meat and influence the hormonal balance of the consumers. There have been only singular reports on modified gender-related behavior or feminization in humans in consequence of soy consumption. In animals, the intake of phytoestrogens was reported to impact fertility, sexual development and behavior. Feminizing effects in humans can be subtle and identifiable only statistically in large populations.

Keywords: phytoestrogens, soy, menopause, nutrition

Zusammenfassung

Phytoöstrogene sind in einigen essbaren Pflanzen enthalten, am reichlichsten in der Soja; sie sind strukturell und funktionell den natürlichen Östrogenen ähnlich. Die Phytoöstrogene werden für den Ausgleich des Hormondefizits in der Menopause verwendet. Gleichzeitig wird die Soja in der Säuglingsnahrung und anderen Lebensmitteln gebraucht. Außerdem wird die Soja als Viehfutter benutzt, sodass die Phytoöstrogene und deren aktive Metaboliten (Equol) im Fleisch verbleiben und die Homöostase der Geschlechtshormone bei den Verbrauchern beeinflussen können. Es gibt nur einzelne Mitteilungen über eine Änderung des geschlechtsassoziierten Verhaltens oder eine feminisierende Wirkung bei Menschen infolge des Sojakonsums. Eine Störung der geschlechtlichen Entwicklung, des Verhaltens und der Fertilität bei Tieren unter der Einwirkung der Phytoöstrogene ist bekannt. Die Feminisierung bei Menschen kann im Einzelfall geringfügig und nur statistisch in größeren Kontingenten nachweisbar sein.

Schlüsselwörter: Phytoöstrogene, Soja, Menopause, Ernährung

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Soy and phytoestrogens

Phytoestrogens are substances of plant origin that are structurally and functionally similar to the estrogens. Among them, isoflavones and coumestans are the most extensively studied groups. Isoflavones are present in different edible plants being most abundant in soy [1], [2], [3]. Consumption of soy products has been associated with favorable health effects; while potential adverse effects can be undervalued [4]. Phytoestrogens are used as a natural alternative to estrogens for replacement therapy in the menopause [1]. Preclinical trials have demonstrated both genomic and non-genomic action of phytoestrogens including selective but weak binding to the estrogen receptors [5]. Some epidemiological studies suggest that dietary intake of phytoestrogens may contribute to the decreased incidence of postmenopausal cardiovascular disease [6] and that phytoestrogens are significantly more effective than placebo in reducing the frequency of hot flashes [7]. Evidence in support of clinically relevant biological effects has, however, been generally rated as insufficient or absent [5], [8], [9], [10], [11], [12], [13], [14]. Recent reviews concluded that in spite of increasing preclinical and clinical studies in the past decade, 'appealing evidence is still lacking to support the overall positive risk-benefit profile of phytoestrogens' [15], that most good studies show no clear benefit from phytooestrogens and some potential for harm [16].

Menopausal hormone therapy remains the only treatment that consistently has a greater effect than placebo on alleviation of menopause-related vasomotor symptoms [16].

Doubts concerning phytoestrogens have increased recently, when a critical analysis of earlier findings from supplementing the diet with soy protein has failed to confirm phytoestrogens as the responsible agent for beneficial cardiovascular effects. Contrasting data have been reported on the potential of phytoestrogens to prevent hormone-dependent cancers (e.g. breast and prostate) and to successfully treat post-menopausal complaints [17]. There is little evidence in support of the hypothesis that phytoestrogens protect against menopausal osteoporosis; published studies had no controls for confounding factors, the observations being generally of short duration [18], [19]. In regard to osteoporosis, the latest review concluded that 'evidence points to a lack of a protective role of soy isoflavones in the prevention of postmenopausal bone loss' [20]; although there is also an opinion that in vitro and animal studies show some benefit from isoflavones, which however has not been clearly confirmed by long-term human trials [21]. There might be genetic differences in this regard, as equol producers seem to present a more positive response to isoflavone intervention [21]. Differences have been reported in the prevalence of the equol-producer phenotype among ethnicities, with a higher prevalence in soy-consuming Asian than in Western populations [22]. It is probably related to eons of adaptation of East Asians to soy. In view of this adaptation, supposed beneficial effects of soy, if even reported in East Asians, should not be automatically extrapolated onto Whites and other peoples, who had historically no contact with soy.

The use of phytoestrogens as an alternative for hormone replacement therapy is not advocated also because of insufficient information on safety [23]. There have been reports on the adverse effects and interactions with drugs [24]. Moreover, soy is known as allergenic food at least for some populations [2], [25]. Finally, it should be mentioned that soybean-based oil emulsions were identified as one of the major causes of cholestasis related to pediatric parenteral nutrition [26].

The biological action of estrogens is mediated by receptors. The question is justified why the incidental plant analogues must be used for replacement therapy instead of right doses of the natural or synthetic hormones that are complimentary to the receptors. If we have keys for the lock, why should we use a screwdriver? The belief that 'natural' medicines have no adverse effect is mistaken [16]. Moreover, commercial preparations often contain a mixture of ingredients of unknown concentrations [27]. It should be remarked about the shotgun remedies containing both phytoestrogens and estrogens [28] that, if phytoestrogens indeed bind selectively to the estrogen receptors [5], they might inhibit the action of the estrogens competing with them for binding sites, which would possibly enhance the required dose or at least make the dose effect more difficult to determine.

Phytoestrogens are used to compensate for hormone deficiency in the menopause; at the same time, their hormonal potential does not prevent from the broad use of soy in infant food, other foodstuff and pediatric parenteral nutrition [26], [29]. Note that consumers are sometimes unable to find out whether a product contains soy, while in some countries e.g. Russia products and their labels correlate poorly, a product with the same label can change its quality etc. Considering extensive use of soy for animal fodder, residual phytoestrogens and their active metabolites such as equol, produced by intestinal bacteria in cattle and domestic fowl [30], [31], can remain in meat and influence the hormonal balance of consumers. Apart from singular reports e.g. on changes of the gender-related behavior in girls [32] or gynecomastia in a man [33] after intake of soy products, no data on modification of gender-related characteristics or feminization in humans in consequence of soy consumption have been found. There was a singular report on an inverse association between soy food intake and sperm concentration in men [34]. Phytoestrogens were reported to exert anti-androgenic effects in patients with castration-resistant prostate cancer [35]. Finally, according to some reports mainly from Asia, reviewed in [36], the phytoestrogens protect against both breast and prostate cancer, which is not readily understandable physiologically and appears to be oversimplification at least. Comparisons were often made between ethnic groups or non-vegetarians vs. vegetarians (assuming that the latter consume more soy) [36], where judgment is probably complicated by confounding factors. If high doses of isoflavones are used for long periods of time, they may stimulate the endometrium and breast; women treated for breast cancer were recommended to avoid them [16]. This topic is however outside the scope of the present letter.

In animals, the intake of phytoestrogens was reported to impact fertility and morphogenesis of ovaries, e.g. 'clover disease' in sheep [15], [37], to be associated with derangements of sexual development in male rats [38] etc. Feminizing in humans can be subtle and identifiable only statistically in large populations. It was argued that phytoestrogens are selective receptor modulators thus acting differently from the natural estrogens, not necessarily feminizing [36], [39]. If even it is so, the question remains whether such modulations are desirable for the infants receiving soy nutrition, for children and other consumers of soy products. The words 'modulation' and 'regulation' are sometimes used to make impression that certain botanicals have beneficial effects, which is groundless. 'Regulation' for the benefit of the human organism presupposes consciousness and will. When it is stated, for example, that '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' [40] 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, os-

teoporosis, cancer, cardiovascular, neurodegenerative, immune and metabolic diseases' [40].

Another example of potential misunderstanding: it was stressed that findings from a recent metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy products affect serum testosterone or estrogen levels in men, which according to the context was meant as a proof for the absence of feminizing effects [36], [39]. In a case report on gynecomastia associated with soy consumption by a man it was noted that after the patient stopped consuming soy products, 'his breast tenderness resolved and his estradiol concentration slowly returned to normal' [33]. It should be commented that, being estrogen analogues, phytoestrogens may exert estrogenic effects on their own independently of the levels of endogenous hormones.

The supposition that botanicals are 'natural' for the human organism can be misleading. It is known that many substances of plant origin are toxic. Marketing of botanicals with unproven effects in the guise of evidence-based medications was commented previously [41]. In this connection, it is sometimes difficult to distinguish between reliable and unreliable publications. For example, a supposed anti-atherogenic effect of phytoestrogens and other botanicals was reported on the basis of experiments with cell monocultures, where the ability of serum to induce accumulation of lipids in the cultured cells was interpreted as an indicator of serum atherogenicity [42], [43]. Anti-atherogenic action of different drugs and botanicals was measured in the cell cultures [44], [45], [46], [47]. However, as discussed previously [41], the relationship between the uptake of lipids by cultured cells and atherogenesis in vivo must be inverse rather than direct. For example, in familial hypercholesterolemia, a genetic defect of lipoprotein receptors results in a reduced uptake of cholesterol by cells and accelerated atherosclerosis [48], [49]. The function of LDL receptors largely determines the concentration of cholesterol-carrying lipoproteins in blood. In tissue cultures, most cells rely on LDL receptors as a source of cholesterol [49]. Accordingly, if a pharmacological agent lowers the uptake of lipids by cells in a culture, it should be expected to increase the blood cholesterol in vivo [50]. This example shows how a spurious theory was used for marketing of botanicals. Following their concept, the same scientists started blood apheresis through a column with immobilized LDL to remove 'non-lipid atherogenicity factors' twice monthly for the period of 7–9 months (Grant 14-15-00112 of the Russian Scientific Foundation) [51]. The studied patients with angina pectoris had normal blood level of cholesterol. In the course of the study, the patients were reported to feel better and endure higher physical loads [51], which could have been caused by a placebo effect. It is known that invasive procedures can be associated with placebo effects [52], [53]. Apheresis is associated with risks [54], although severe side-effects are very rare [55]. Beneficial effect of the apheresis in [51] cannot be excluded a priori, although this procedure is usually aimed at removal of lipoproteins, for example, in patients with severe drug-resistant LDL-hypercholesterolemia or lipoprotein elevation and premature atherosclerosis [56], [57].

Conclusion

Phytoestrogens are present in different edible plants being most abundant in soy; among others, they are used to compensate for estrogen deficiency in menopause. However, the estrogenic potential of phytoestrogens does not prevent from extensive use of soy in infant food and other foodstuffs as well as pediatric parenteral nutrition. Feminizing effect of phytoestrogens and soy products may be subtle, detectable only statistically in 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.

Notes

Competing interests

The author declares that he has no competing interests.

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