Phytoestrogens

This article has been translated from WikiSkripta; ready for the **editor's review**.

Phytoestrogens are substances originating from the plant kingdom, whose structure is similar to endogenous estrogens produced in the human body. The word "phytoestrogen" comes from the Greek phyto = plant and estrogen = hormone.

Their structure and size are primarily similar to endogenous 17-β estradiol, and it is precisely because of this similarity that they can bind to estrogen receptors (https://en.wikipedia.org/wiki/Estrogen_receptor) and, due to their estrogenic or anti-estrogenic effect, lead to estrogen-dependent (estrogen-dependent) transcription. For this reason, they are often used as a natural alternative in hormonal treatment. [1] [2] [3] In the plant kingdom, phytoestrogens are produced by plants as low-molecular substances, and only in certain situations, such as when attacked by pests (fungistatic, antibacterial, antiviral, antioxidant functions) or during other forms of stress. [1] [4]

They can interfere with the metabolism of endogenous estrogen, for example by inhibiting the aromatase enzyme, which can help prevent breast and prostate cancer. [2]

History

Red clover story (Clover disease) - Red clover (https://en.wikipedia.org/wiki/Trifolium_pratense) (Trifolium pratense) has been cultivated in Europe since the third or fourth century. At the end of World War I, red clover was considered a vegetable substitute due to food shortages in Germany. Various toxicological studies began to take place during this period, one of which (Australia) was the first to demonstrate that red clover has estrogenic activity. Fertility problems in sheep grazed on red clover pastures have been attributed to isoflavones and coumestrol.

As early as the 1950s, isoflavones from red clover were identified as estrogen activators. Pope et al. already in 1965 he isolated biochanin A from red clover. Schultz proved that biochanin A and formononetin belong to the glycosides of red clover. In the 60s and 70s of the 20th century, chromatographic and spectrophotometric methods for the determination of isoflavones were created (nowadays, the RPHPLC = reversed phase-high performance liquid chromatography method is used for the determination of isoflavones in red clover).

Other problems with severe infertility in cattle caused by estrogen stimulation with red clover were noted in the early 1970s and 1980s.

In the 1980s, the anticarcinogenic effect of biochanin A was demonstrated, which reduces the amount of [3H]benzo[a]pyrene (https://en.wikipedia.org/wiki/Benzo(a)pyrene) bound to DNA and also limits the metabolism of [3H]benzo[a]pyrene in mammary cells. [2]

Metabolism od isoflavonoids and effect on the cell

After the intake of phytoestrogens in the diet, which is mostly in the form of glycosides (https://en.wikipedia.org/wiki/Glycoside) (β-glycosides; this means that a carbohydrate unit is attached to a structure called an aglycon), carbohydrate residues are hydrolytically broken down in the gastrointestinal tract with the help of intestinal microbiota and endogenous enzymes (hydrolase, β -glucosidase). This leads to the formation of aglycones (which occurs most in the area of the stomach), which can be resorbed through the intestinal wall. If phytoestrogens are taken in the diet already in aglycated form, they are absorbed directly, namely in the proximal part of the duodenum. [1][5]Glucuronidation takes place in the enterocyte, then it passes through the cell membrane into the blood and binds to albumin in the blood, or reacts with lipoproteins. It passes to the liver, where it reacts with glucuronic acid and sulfates (conjugation reaction; for example, various enzymes such as sulfotransferase, β-glucuronidase). These conjugates can be excreted in bile or urine. When excreted in the bile, they undergo enterohepatic circulation. [2] [6]

Phytoestrogens bind to estrogen receptors, they are able to do so due to a structure similar to 17β-estradiol. Phytoestrogens are classified (although their mechanism of action is different) among the so-called natural SERMs (selective estrogen receptor modulators), which is a group of phytopharmaceuticals that act as receptor agonists in some tissues and as antagonists in other tissues. For phytoestrogens, their tissue specificity depends on the relative amounts of ER-α and ER-β, on the affinity for ER-α and ER-β, and on the activity of the substances required to mediate the reaction. [2]

Estrogen receptors are located inside animal cells and function as transcription factors – after ligand binding, they change their structure to dimers, move to the cell nucleus, and there bind to estrogen-responsive sites (ERE) on DNA and affect transcription (genomic nature of the reaction).[3] These receptors exist in two subtypes ER-α and ER-β. ER-α is mainly found in the cells of the uterus, ovaries, breasts, testicles, bones, liver, white adipose tissue and some parts of the brain. ER-β is also found in the testicles, ovaries, bones, some parts of the brain, and then in the prostate, colon and salivary glands.[7] Phytoestrogens have different affinity (https://en.wikipedia.org/wiki/Ligand_(biochemistry)) for the ER-α and ER-β receptor subtypes, with a lower affinity for the ER-α subtype (they can show an affinity of up to 5x higher for the ER-β isoform). Thus, phytoestrogens are thought to mediate their effect primarily through ER-β.[2][8] Compared to endogenous estrogen, phytoestrogens have a 1,000x to 10,000x lower

relative binding affinity (willingness to bind) to the ER, but they can reach higher concentrations in the blood than endogenous estrogen. [3] Although α and β receptors can be found in the same tissues, their application, quantity and role in development can be different. The type of tissue, the age of the individual, the animal species and other factors influence their representation. [9] Together, they participate in the development of ovarian follicles, breast tissue cells, smooth muscle, heart muscle and vascular endothelium cells. ER-α is then important for the production of lutropin and follitropin and ER-β for the development of memory, learning and for the maintenance of bone mass in women. In addition to the ER inside the cell, it can be found at about 2-3% on the cell surface, where they then mediate a non-genomic reaction (regulation of the cell cycle, influence on the function of cell proteins, antioxidant effect). [2] [10] A reaction of a genomic nature affects the number of proteins produced; reactions of a non-genomic nature then protein activity. In addition to estrogenic and anti-estrogenic activities, phytoestrogens can also exhibit androgenic activity (binding to androgen receptors, the transcription of androgen-dependent genes is reduced, which can probably lead to a decrease in sensitivity to androgens from the blood and thus prevent prostate hyperplasia) and progesterone (progesterone receptors , a progesterone reaction occurs).[2][4]

By stimulating proteosynthesis in the liver, phytoestrogens can increase the level of blood proteins that are used to bind sex hormones (SHBG = sex hormone binding globulin) and thus reduce the concentration of active hormones. In high concentrations, they act as antioxidants. Furthermore, they have an effect on the inhibition of the cell's signaling pathway.[3]

Effect on the metabolism of steroid hormones

After binding of phytoestrogens to receptors on the surface of cells, a whole range of steroid metabolism enzymes can be inhibited. As a result, it is not possible to synthesize these hormones and the level of active steroid hormones in the given tissue decreases.[3] The intervention of phytoestrogens in the metabolism of endogenous estrogen (by inhibiting the aromatase enzyme, which is the cause of 60% of breast cancer in women) can act in the prevention of breast cancer. Aromatase inhibition is mainly possible with flavones (genistein). Furthermore, coumestrol and biochanin A inhibit enzymes (more precisely, variants of the 17β-HSD enzyme) interfering with the metabolism of androgens and estrogens, which has an effect on prostate growth.[2]

Types of phytoestrogens

Phytoestrogens are divided according to their chemical structure. The division is not uniform and differs from one author to another. For example, Mikscik divides phytoestrogens into six groups: coumestans, resorcylic acid lactones, isoflavones, flavones, flavonones and chalcones. [11] Other authors divide phytoestrogens into the following four groups: isoflavones, prenylflavonoids, pterocarpans, lignans.[12] A narrower division includes only isoflavones, coumestans, lignans. According to most authors, four groups of phytoestrogens are considered and are the most discussed:[10][13][14]

- isoflavones
- coumestanes
- lignans
- stilbenes

Isoflavones

The best-known group of phytoestrogens are isoflavones, which are naturally found mainly in legumes (legume family, Fabaceae). The most important is the content in soy and soy products, where the isoflavone daizein is mainly found. Soy products such as tofu, tempeh, soy milk and soy flour are considered rich sources of isoflavones. In contrast, soy sauce and soy oil do not contain any isoflavones.[15]

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The group of isoflavones also includes genistein, formononetin, glycitein and biochanin A. [12]
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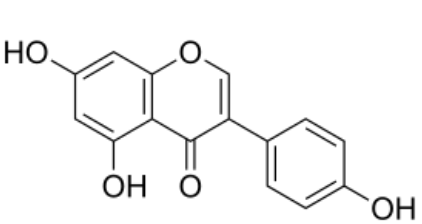
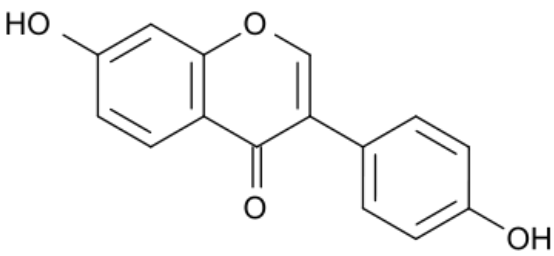
Sometimes the substance equol is included among the isoflavones, even though it is not a phytoestrogen, but a metabolite created from daizein by the action of intestinal bacteria. It has a stronger and longer-lasting effect than other isoflavones.

In addition, isoflavones are found in clover, rye and some fruits.[14]

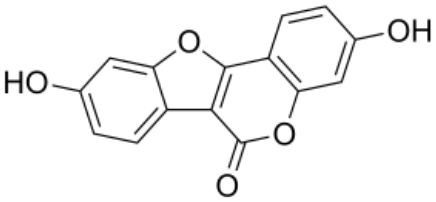




Coumestanes

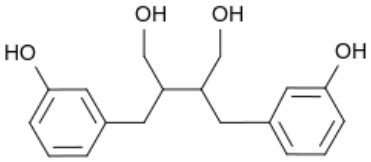
Coumestanes, derivatives of coumarin, form a large group of chemical substances, but only some of them show estrogenic character.[16] Compared to the group of isoflavones, they have stronger estrogenic activity.[12]

The most important representative is coumestrol, which is the main phytoestrogen of alfalfa[14] The main food source is legumes. It is reported that the highest content is in clover and soybean sprouts.[16] During germination, its content increases several times (70-150x).[12]



Lignans

Lignans are classified as polyphenolic compounds. The most important representatives are syringiresinol, pinoresinol, lariciresinol, isolariciresinol, matairesinol and secoisolariciresinol. The last two representatives do not show estrogenic activity, but in the digestive tract they are transformed into estrogenic active substances enterolactone and enterodiol under the influence of intestinal bacteria.[16] Lignans are widely represented in plants. The largest food sources are flax and sesame seeds, whole grain cereal products, rice, legumes, vegetables, and to a lesser extent fruits.[12]They are also present in green and black tea.[13]



Stilbenes

Stilbenes, like lignans, are classified as phenylpropanoids. The best-known representative of this group is resveratrol, which is represented to the greatest extent in the skin of the blue berries of the grapevine (which is why it is also found in red wine). The pulp contains a negligible amount. Another source of stilbenes is peanuts.

A distinction is made between the cis and trans forms, with only trans-resveratrol exhibiting estrogenic activity. White wine contains a significantly lower amount of trans-resveratrol (0-0.3 mg/l) compared to red wine, where it can contain up to 14.5 mg/l depending on various factors such as the wine variety, geographical conditions, processing, fermentation time. The longer the fermentation takes place, the more trans-resveratrol will be in the final product. [10] Resveratrol

Dietary sources of phytoestrogens

Fytoestrogeny se nachází jak v potravinách rostlinného původu, tak v potravinách živočišného původu, kam se dostaly prostřednictvím pastvy, resp. příjmu krmiva.

Phytoestrogens are found both in foods of plant origin and in foods of animal origin, where they have reached through grazing or feed intake.

Phytoestrogen content in foods of animal origin[17]

Foodstuff	Phytoestrogen content (µg/100 g)
Soy yoghurt	8286
Soy milk	6028
Soy meatballs	4430
Cheese camembert	29
Cheese gouda	24
Yoghurt	20
Skimmed milk	20
Whole milk	12
Butter	11–17
Egg	11
Cream	8
Beef	7–19
Goat milk	5
Pork	4–20
Fish and sea food	2–9

Content (mg/kg) of daidzein, genistein, glycitein and coumestrol in soy and soy products[18]

Foodstuff	Daidzein	Genistein	Glycitein	Coumestrol
Soy	566	442	28,1	0,015
Soy milk	9,2	18	1,7	0,006
Soy sprouts	2,7	5,1	0,045	-
Tempeh	69,4	107	5,7	0,006
Tofu	93,4	170	7,3	0,007
Miso	44,2	59	8	0,024
Soy protein	25,3	59,7	3,1	0,005

Functions of phytoestrogens in plants

Phytoestrogens, as active substances, fulfill a protection and defense function in plants. They protect the plant from the harmful effect of pathogens - they have anti-parasitic, antibacterial, antiviral and fungistatic effects.[19]

Isoflavones are the best-known and best-studied group of phytoestrogens. They also act as antioxidants in plants. Isoflavones with two hydroxyl groups (e.g. daidzein) show the highest antioxidant activity and thus protect the plant from the harmful effects of sunlight. Isoflavones are also responsible for the bitter taste of soy products.[12]

Effects of phytoestrogens on human health

The effects of phytoestrogens on human health are constantly debated.

Due to their antioxidant activity and ability to bind to estrogen and androgen receptors, phytoestrogens can affect the cardiovascular, musculoskeletal and reproductive systems. Furthermore, phytoestrogens have an effect on cognitive function, thyroid gland activity, obesity and cancer. However, most studies examine the effects of phytoestrogens on postmenopausal women.

Based on the observation of a population of women from Southeast Asia, where the intake of isoflavones from soy is high, the use of phytoestrogens in human medicine began to be considered, because women from these regions showed a lower incidence of climacteric syndrome (https://medical-dictionary.thefreedictionary.com/climacteric+syndrome) and osteoporosis, compared to European and American populations. A reduced incidence of breast cancer and a reduced incidence of prostate cancer were also found in Southeast Asian women.[19]

Phytoestrogens mainly act additively. If there is a low level of endogenous estrogens (estradiol) in the body, they bind to estrogen receptors; and conversely, if the level of endogenous estrogens is high (in women of reproductive age), phytoestrogens act antagonistically. [12]

The potential risks or benefits of phytoestrogens depend mainly on the type of phytoestrogens consumed, the size of the dose, the duration of consumption, the age of the consumer and the composition of the diet.

Menopause

The climacteric (https://en.wikipedia.org/wiki/Menopause) period (transition, menopause) is characterized by climacteric syndrome in many women, which is induced by a lack of estrogen. About 80% of women suffer from climacteric syndrome.

In the treatment of climacteric syndrome, lifestyle changes (exercise, balanced diet, avoidance of alcohol and tobacco products) and hormone replacement therapy (HRT (https://en.wikipedia.org/wiki/Hormone_replacement_therapy)) are used. However, HRT has been found to slightly increase the risk of breast cancer and cardiovascular disease.[20]

Phytoestrogens can be used as an alternative in the treatment of climacteric syndrome in women who cannot or do not want to take HRT.[21]

Effect on bone metabolism during menopause

In postmenopause, the protective effect of endogenous estrogens on bone is lost, and over time, postmenopausal osteoporosis may develop with the risk of acute fractures.[19]

Phytoestrogens have a potential osteoprotective effect. Isoflavones, which are most commonly used to treat menopausal symptoms, act on bone via steroid β-ER (the most abundant). They increase the synthesis of vitamin D, the deposition of calcium in the bones, increase the proliferation and differentiation of osteoblasts.[21] At the same time, they reduce the breakdown of bone tissue by osteoclasts. Another osteoprotective mechanism of isoflavones is the reduction of urinary calcium excretion.[22]

A meta-analysis (Cornwell et. al.) from 2004 dealing with the effect of phytoestrogens on human health confirmed a positive effect on bone mass in 11 of the 15 studies evaluated.[10] Baber's meta-analysis from 2010 examined 12 studies of which 7 has shown a positive effect on bone health.[23] Beck also pointed out the positive effect of phytoestrogens in postmenopausal women. In women, there was an increase in bone density and a reduction in bone loss. [2]

A 2013 meta-analysis confirmed the preventive effect of isoflavones in bone protection in in vivo animal studies. Clinical studies have indicated that isoflavones help premenopausal women maintain so-called peak bone mass (https://en.wikipedia.org/wiki/Peak_bone_mass). Isoflavones may also have a slightly positive benefit after menopause, but causality between isoflavone intake and reduced fracture incidence has not been demonstrated.[22]

Based on the studies, however, it is difficult to determine which preparations and in what doses are needed to achieve the desired effect. There may be differences in bioavailability between different dietary supplements, foods, and isolated phytoestrogens that are difficult to account for in studies. Interindividual variability also plays a role, which affects the conversion of isoflavones into biologically effective metabolites. Therefore, it is not possible to unequivocally confirm the beneficial effect of phytoestrogens on bone mineral density and on the prevention of fractures.[21]

Effect on the skin during menopause

Estrogens significantly influence the properties of the skin and its derivatives. A decrease in the level of estrogen during menopause can result in drying of the skin, a decrease in its elasticity and the subsequent formation of wrinkles. There may also be a change in its pigmentation and sensitivity. Thinning of the skin occurs, which leads to increased irritation of the nerve endings and the skin becomes more sensitive.

Phytoestrogens can act on the skin through estrogen receptors or through increased production of certain skin components. Isoflavones clearly improve blood circulation in the skin due to increased vascularization and improve its hydration due to increased production of hyaluronic acid (https://en.wikipedia.org/wiki/Hyaluronic_acid). It also increases the thickness of the skin through the increased production of collagen and elastic fibers. They can have a positive effect on hair growth.[19][23]

Oncological diseases

Epidemiological data and case-control studies have confirmed that countries with a higher intake of isoflavones have a lower incidence of breast and prostate cancer compared to countries with a lower intake of phytoestrogens.[21]

In a well-known study by the American Institute for Cancer Research (AICR), they found that Asian immigrants living in the US have an increased risk of developing cancer compared to the population living in Asia. Increased cancer risk was correlated with length of time in the US and exposure to a North American diet, which contains less phytoestrogens, compared to a typical Asian diet high in soy and soy products. [10]

The effects of phytoestrogens on various cancers can be attributed to a number of mechanisms. Phytoestrogens can inhibit the activity of the aromatase enzyme, which ensures the synthesis of estrogens, which explains their antitumor effect on estrogen-dependent tissues (e.g. breast tissue).[13] The isoflavones genistein and biochanin A are competitive inhibitors of 5-alpha -reductases. Inhibition of this enzyme is used in the treatment of prostate hyperplasia and cancer. Genistein, daidzein and biochanin A induce apoptosis and inhibit the growth of T-47D (https://en.wikipedia.org/wiki/T-47D) and MCF-7 (https://en.wikipedia.org/wiki/MCF-7) breast tumor cells in vitro. [24]

Phytoestrogens can inhibit enzymes associated with cell growth (DNA-topoisomerase, ornithine decarboxylase, protein tyrosine kinase) and can thus inhibit the proliferation of tumor cells.[14] Their antioxidant activity can also be used.

The protective effect of phytoestrogens on the development of cancer is still a matter of debate. Although studies in vitro and in vivo point to the beneficial effects of phytoestrogens, studies on human subjects do not have convincing conclusions confirming clearly positive effects.[25] Long-term consumption of isoflavones is considered safe in relation to the breasts and uterus, as there is no increase in the mammographic density of breast tissue (increased breast density would increase the risk of breast cancer) and there was no effect on the mucosa of the uterus.[20]

Cardiovascular diseases

The beneficial effect of phytoestrogens on the function of the heart and blood vessels is mediated by β-ER, which is found in the heart and blood vessels.[24] In addition, isoflavones stimulate the activity of the enzyme NO-synthase and thus indirectly support vasodilation.[20] E.g. genistein demonstrates a direct vasodilating and anti-aggregation effect.[24] Several studies confirm the beneficial effects of isoflavones on the concentration and composition of blood lipids, the reduction of LDL-cholesterol and triacylglycerols and the increase of HDL-cholesterol concentration. However, some studies have not confirmed these findings.[20] Other studies claim that the positive effect is due to the soy protein itself.

The authors of some studies derive the cardioprotective effect of phytoestrogens from their antioxidant properties. Isoflavones have the ability to stabilize LDL lipoproteins from oxidation, which is believed to be one of the possible causes of atherosclerosis.[14]

Many cardiologists point to the beneficial effect of resveratrol from red wine on cardiovascular health. This assumption has not yet been confirmed by scientific studies. Most studies used concentrated dietary supplements, so it is not possible to relate the positive effects of resveratrol to wine alone. There are even discussions that ethanol itself is responsible for improving the condition of blood vessels. Although no study has confirmed the positive effect of resveratrol on cardiovascular function, red wine consumption is still associated with the French paradox (https://en.wikipedia.org/wiki/French_paradox). [10]

Negative effects of phytoestrogens on health

Phytoestrogens have been known as so-called endocrine disruptors (https://en.wikipedia.org/wiki/Endocrine_disruptor) since the 1940s, when a high incidence of infertility and abortions was recorded in Australia in sheep grazed on pastures with clover. This mechanism of action has already been confirmed in several studies on vertebrates. The effects were manifested by an increase in miscarriages, infertility, death or malformations of the fetus.

Adverse effects are minimal in postmenopausal women, but may pose a risk to infants, women of reproductive age, and pregnant women. They can induce irregularity in the menstrual cycle and cause premature onset of puberty in children. This risk should be considered in newborns who are fed soy-based breast milk substitutes. Some studies have noted menstrual cycle disturbances in women who were fed soy-based infant formula; but other studies did not confirm a similar effect. So it's not entirely clear whether soy consumption in newborns can have long-term negative health effects, but parents need to be aware of the possible estrogenic effects of soy formula.

Phytoestrogens can also affect the thyroid gland – genistein and daidzein can induce hypothyroidism and associated goiter, and can also block thyroxine synthesis. That is why soy is referred to as a strumigen. Therefore, adequate iodine intake is ensured during regular consumption of soy. Knowledge about the relationship between soy consumption and thyroid hormone levels in pregnant women is very limited. Nevertheless, it is advisable to consider the possible strimogenic effects of phytoestrogens in pregnant women, since thyroid hormones are necessary for the proper development of the fetal brain.[26]

Resources

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