ClinicSearch

Clinical Trials and Case Studies

Elizaveta I Bon *

Open Access

Review Article

Effect of Plant Analogues of Estrogens on the work of the Hypothalamic-Pituitary System

Maksimovich N.Ye, Bon L.I *, Yankovskii R.A

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

***Correspondence Author:** Elizaveta I Bon, Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

Received Date: June 20, 2024 | Accepted Date: July 10, 2024 | Published Date: July 25, 2024

Citation: Maksimovich N.Ye, Bon L.I, Yankovskii R.A (2024), Effect of Plant Analogues of Estrogens on the work of the Hypothalamic-Pituitary System, *Clinical Trials and Clinical Research*, 3(4); **DOI:**10.31579/2835-835X/070

Abstract:

There are different opinions about phytoestrogens (hereinafter PhE): some consider them a panacea for the whole complex of women's diseases, a vitamin of youth, while others indicate the presence of side effects of these substances, an ambiguous effect and low effectiveness. PHE is similar in chemical structure to native estrogens, which determines their affinity with estrogen receptors, which allows them to be included in the natural metabolic processes in the body, affecting hormone metabolism and the processes of maintaining homeostasis.

Keywords: phytoestrogens; endocrine disrupting chemicals; isoflavanoids; coumestanes; lignans; estrogen receptors; diabetes mellitus; obesity

Introduction

Useful properties of plants have been known to mankind since ancient times. For thousands of years, they served not only as food, but also helped in the treatment of various diseases.

Relatively recently, in the 1930s, scientists began actively studying a fundamentally new class of organic compounds – phytoestrogens (PhE). [1]

It should be noted that PhE is not an independent class of organic compounds. In terms of their effect on the endocrine system, these compounds belong to an extensive class of “endocrine system effectors” (option for CIS-countries) [2]. Effectors of the endocrine system affect the endocrine system, acting as xenobiotics [2]. According to the classification, endocrine effectors are divided into anthropogenic (by-products of human industrial activity), medicinal (contained in medicines) and PhE [2]. This classification is not widely used in the West, where it is customary to use either a clinical classification or an evidence-based one [3,4]. The English-language equivalent of the term endocrine system effectors is “endocrine disrupting chemicals”, which literally translates to “substances that destroy the endocrine system” or “endocrine disruptors” [5]. The latter term has become increasingly used in russian-language literature. Initially, western scientists believed that endocrine effectors only damage the endocrine system, causing malignant neoplasms [6,7], but in more recent articles, western scientists offer therapy with endocrine effectors, in particular phytoestrogens, not only for oncological diseases, but also for certain pathologies of carbohydrate metabolism [8].

History of the study of phytoestrogens. The first mention of PhE dates back to 1899 in the work of A. G. Perkin and F. G. Newbury, devoted to the properties of the dyer's broom (Genistatinctoria) and heather (Calluna vulgaris).

And only 27 years later, in 1926, scientists again returned to the study of phytoestrogens. This was associated with reduced fertility in some animals. So, for example, breeding cheetahs in nurseries, in order to restore their population, soybeans were added to the diet. This was reflected in a decrease in their fertility. Another example concerns austrian sheep that ate clover, which affected their fertility. [9]

In 2006, L. W. Thomson and B. A. Booker published a study according to which the list of foods containing PhE is headed by nuts and oil seeds. They are followed by soy products, cereals and bread with bran, legumes, meat and other food products [3].

Current research is aimed at clarifying the chemical structure of individual phytoestrogens and their mechanisms of action.

Classification of phytoestrogens. Further refinement of the chemical structure of phytoestrogens made it possible to divide them into 3 broad groups: isoflavanoids (genistein, daizein, glycitein, biochanin); coumestanes (coumestrol, vedelolactone, plicadin); lignans (enterodiol, enterolactone, pinoresinol, etc.) [10]. It should be noted that the consumption of soy rich in isoflavans and lignans increases with the numerical growth.

Mechanisms of action. Until recently, it was believed that the only way phytoestrogens interact with the human body is through interaction with estrogen receptors. To date, this path is not the only one, but it is the main one.

The chemical structure of phytoestrogens is extremely similar to that of human endogenous estrogens. Two types of estrogen receptors are found in humans: alpha (ERα) and beta (ERβ). ERα is mainly localized in the female genital organs, while ERβ is located in other organs [11]. This ubiquitous location of estrogen receptors determines the multi-organ

effect of estrogens on a woman's body. It has been proven that ERα enhances the growth and proliferation of cell populations [12], while ERβ, on the contrary, inhibits these processes [13], which makes ERα and ERβ antagonists. Strom A. in 2004 showed in his experiments on pure breast cancer cell lines that genistein and estradiol in the expression of ERα induce a concentration-dependent increase in proliferation and, conversely, in the expression of ERβ – don't cause cell growth and proliferation [15]. With the growth of a malignant neoplasm, for example, a breast, activation of ERα will be an undesirable effect. Thus, more than 65% of breast tumors respond to antiestrogen therapy [14].

The affinity of phytoestrogens to estrogen receptors is not uniform and depends on their chemical structure, the concentration of native estrogens, and the predominant fraction of estrogen receptors. Thus, genistein will have different effects, for example, on the mammary gland, in which ERα prevails, and, for example, on the prostate (ERβ prevails) [16]. It should also be noted that the affinity of phytoestrogens compared to endogenous estradiol is less than 1%, and their affinity for ERβ is higher than for ERα.

Another possible mechanism of action according to Dolinoy D.Y. et al. (2006) is DNA methylation in the offspring of mice. Virgin female mice were fed a phytoestrogen diet 2 weeks before mating, then during pregnancy and when feeding their young. As a result of the experiment, the offspring of female mice on a phytoestrogen diet showed a change in color and a significant effect on the color change of the offspring of mice was proved. [17]

Hilakivi-Clarkel and etc. (2010) reports on the role of genomic changes in reducing cancer risk with genistein [18], and Ramali (2015) provides statistical data on the relationship between genome modification caused by phytoestrogens and reducing the risk of obesity [19]. DNA methylation causes certain genes to become unavailable for transcription. This leads to inhibition of adipocyte division in the first year of life, which significantly reduces the risk of obesity [8].

Inhibition of kinases by phytoestrogens may also be a likely mechanism of their action [20]. A large number of protein kinases are encoded in the human genome, and a violation of their transcription will lead to the onset of the disease.

According to Jungbauer A. and Medjakovik S. (2014), the likely mechanism of action is the effect on receptors activated by peroxisomal proliferates (RAPP) [21]. RAPPs are nuclear receptors that are transcription factors [22]. There are 5 types of RAPPs have been identified: α, β/Δ, ɣ-1, ɣ-2, and ɣ-3, each of which is refractory to certain organs and tissues [23]. Activation of RAPPs can either increase or decrease the expression of transcription genes. Thus, RAPP regulates metabolism in specific tissues, for example, an increase in the concentration of free fatty acids activates RAPP-ɣ-2, which leads to increased metabolism in adipocytes. Presumably, phytoestrogens have a certain affinity for RAPP- α and RAPP- ɣ, which explains the statistical relief of diabetes mellitus type 2 in people taking products with phytoestrogens in high concentrations [24]. Perhaps this mechanism is responsible for the reduction of obesity [8].

Some researchers suggest that phytoestrogens act through the activation of AMP-activated protein kinase [25]. In vitro experiments vitro have shown an association between an increased amount of phytoestrogens and activation of AMP-activated protein kinase. The exact mechanism of this phenomenon is unknown, but it is suggested that this mechanism may be implemented in connection with phytoestrogen-mediated stimulation of intracellular reactive oxygen species [25].

Receipt paths. The most frequent route of intake of phytoestrogens is alimentary. Phytoestrogens are absorbed in the gut, but bacteria can convert daidzein (a poorly digested phytoestrogen) into equol. It turns out that approximately half of the population has an intestinal flora capable of producing equol [26]. Back in the 60s of the last century, it was shown that the intestinal flora is responsible for the production of equol [27], and it was proved that bacteria capable of synthesizing equol are present only in women [28]. These are representatives of the genera Clostridium, Fecalibacteria, and Colinciella [29]. It should be noted that, unlike humans, absolutely all rodents and horses are able to synthesize equol, which casts doubt on the possibility of comparing the effects of phytoestrogens in these animals with humans [30]. In humans, enterolignans are metabolites of the intestinal biota [31].

The effect of phytoestrogens on sex hormones is realized through the main mechanism of action, that is, interaction with estrogen receptors. Thus, the influence on the hypothalamic-pituitary system is carried out, within which the hypothalamic-pituitary-gonadal axis (HPGA) and the hypothalamic-pituitary-thyroid axis (GPTA) are distinguished.

GPTA controls the secretion of estrogen. When there is insufficient estradiol, the hypothalamus releases follicle-stimulating hormone and luteinizing hormone, which promote follicle maturation and estradiol synthesis [33]. When estradiol levels drop , it is a trigger for follicule-stimulating hormone (FSH) and luteinizing hormone (LH) realization by the hypothalamus [34]. Thus, phytoestrogens can regulate FSH and LH levels through ER.

На беременных женщин Phytoestrogens don't affect pregnant women. It has been shown that the blood of women taking PhE during pregnancy has a normal level of estradiol in the blood [35].

Phytoestrogens also do not significantly affect infants [36], even though their bodies are more sensitive to exogenous factors during this period of life. However, according to some data, girls who take phytoestrogens in preschool age are prone to early puberty [37]. An increased amount of estrogens in boys can lead to its subsequent development in the female type [37].

An extremely important clinical effect is the postmenopausal endowment associated with the inability to synthesize estradiol in the required volume. In response to this failure of the ovary, the hypothalamus implements FSH and LH, and their concentration increases. In high doses, FSH and LH determine the symptoms of menopause: headaches, neurosis, brittle bones, hair, sagging skin, although the latter is most likely associated with a lack of estradiol. Phytoestrogens, through their effect on ER, reduce the production of FSH and LH, which eases the menopausal symptom. [43]

However, according to the 2008 RQS, phytoestrogens increase the risk of breast cancer in european women[39], which is not the case for Asian women (2009 RQS) [40].

In men, phytoestrogens contribute to reducing the risk of prostate cancer [41], which is most likely due to their mechanism of action through ER. Prostate cancer is mainly mediated by a high content of androgens, while phytoestrogens reduce the concentration of male sex hormones.

There are no unambiguous data on the effect of phytoestrogens on GPTA [42,43]. A 2011 RQS [44] shows an insignificant association of less than 10% of women with relief of hypothyroidism due to the use of phytoestrogens, provided that the iodine content in the diet is normal. The exact effect of phytoestrogens on thyrocytes or mediated mechanisms of influence has not been established [43].

There are no data on the effect of phytoestrogens on thyroid hormones in pregnant women [45].

A mass screening of children in the Czech Republic in 2006 showed an increase in free thyroxine in the blood due to the intake of phytosetrogens [46]. According to Conrad S. S., Chiu H., Silverman B. L. (2004), children with congenital hypothyroidism showed an increase in the production of thyroid hormones when taking phytoestrogens [47], but this is not confirmed by newer studies [48].

Conclusion: Thus, despite the fact that phytoestrogens themselves can cause malignant neoplasms, they are quite a promising direction in hormone replacement therapy. It is worth noting that breast cancer is mainly observed in european women, who are not characterized by the use of phytoestrogen-containing products.

The main mechanism of action mediated by the effect on estrogen receptors, most likely, was "developed" by plants to reduce the fertility of the animal population in order to spread phytoestrogen-containing plants, today it can not only help in relieving postmenopausal symptoms, but also in the treatment of pathologies of carbohydrate metabolism, some malignant neoplasms within the framework of the influence on the hypothalamic-pituitary-the gonadal axis.

Although the effect of phytoestrogens on the hypothalamic-pituitary-thyroid axis has not been proven, this direction remains promising due to the small amount of literature, which is completely contradictory.

References:

1. Viggiani, M.T. (2019). Phytoestrogens: Dietary intake, bioavailability, and protective mechanisms against colorectal neoproliferative lesions. Barone [eds]. – Text: direct *Nutrients*. –. – N 8. - P. 1709 – 1729.
2. Lizneva, D. V., Sinitsyna, A. I. (2012). Influence ofxenoestrogens, phytoestrogens, medicinal estrogens on human reproductive and somatic health Problems of reproduction. –. - No. 4. - p. 16-22.
3. Dickerson S. M., Gore AC (2007) Estrogenic chemical effects that destroy the endocrine system on reproductive neuroendocrine function and dysfunction throughout the entire life cycle. *Reverend Endocrus Metab Disord*. 8:143-159
4. Anway MD, Skinner MK (2006) Epigenetic transgenerational actions of endocrine disruptors. *Endocrinology* 147: S43-S49
5. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, et al. (2015). EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev*; 36(6): E1–E150.
6. Sirotkin AV, Harrath AH. (2014). *Phytoestrogens and their effects;* 741:230–236.
7. Sirtori CR, Arnoldi A, Johnson SK. (2005). Phytoestrogens:end of a tale?Annals of medicine; 37(6):423–438.
8. Dalamaga M, Kounatidis D, Tsilingiris D, Vallianou NG, Karampela I, et al. (2024). The Role of Endocrine Disruptors Bisphenols and Phthalates in Obesity: Current Evidence, Perspectives and Controversies. *Int J Mol Sci* ;25(1):675.
9. Alefirov A. N. (2010). Phytoestrogens in oncology. Lecture No. 18. / XVII Russian National Congress "*Man and Medicine", Moscow*, 12-16. 04.
10. Domínguez-López I, Yago-Aragón M, Salas-Huetos A, Tresserra-Rimbau A, Hurtado-Barroso S. (2020). Effects of Dietary Phytoestrogens on Hormones throughout a Human Lifespan: A Review. *Nutrients*;12(8):2456.
11. Kuiper GGJM, Enmark E, PeltoHuikko M, Nilsson S, Gustafsson JA. (1996). Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *P Natl Acad Sci USA*; 93: 5925–5930.
12. Williams C, Edvardsson K, Lewandowski SA, Strom A, Gustafsson JA. (2008). A genome-wide study of the repressive effects of estrogen receptor beta on estrogen receptor alpha signaling in breast cancer cells. *Oncogene* 27: 1019–1032.
13. Stossi F, Barnett DH, Frasor J, Komm B, Lyttle CR, Katzenellenbogen BS (2004). Transcriptional profiling of estrogen-regulated gene expression via estrogen receptor (ER) alpha or ERbeta in human osteosarcoma cells: distinct and common target genes for these receptors. *Endocrinology* 145: 3473–3486.
14. Ali S, Coombes RC. (2000). Estrogen receptor alpha in human breast cancer: occurrence and significance. *J Mammary Gland Biol Neoplasia;* 5: 271–281.
15. Strom A, Hartman J, Foster JS, Kietz S, Wimalasena J, et al. (2004). Estrogen receptor beta inhibits 17beta-estradiol-stimulated proliferation of the breast cancer cell line T47D. *Proc Natl Acad Sci U S A* 101: 1566–1571.
16. Pearce ST, Jordan VC. (2004). The biological role of estrogen receptors alpha and beta in cancer. *Crit Rev Oncol Hematol* 50: 3–22.
17. Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL. (2006). Maternal genistein alters coat color and protects A(vy) mouse offspring from obesity by modifying the fetal epigenome. *Environ Health Persp* 114: 567–572.
18. Hilakivi-Clarke L, Andrade JE, Helferich W. (2010). Is soy consumption good or bad for the breast? *J Nutr* 140: 2326S–2334S.
19. Remeli M., de la Garza A. L., Magnit Yu., Aumuller E., Haslberger AG. et al. (2015). Obesity: epigenetic regulation-recent observations . *Concepts of biomol* 6: 163-175.
20. Dubey RK, Gillespie DG, Imthurn B, Rosselli M, Jackson EK, et al. (1999). Phytoestrogens inhibit growth and MAP kinase activity in human aortic smooth muscle cells. *Hypertension;* 33: 177–182.
21. Jungbauer A, Medjakovic S. (2014). Phytoestrogens and the metabolic syndrome. *J Steroid Biochem Mol Biol*. 139: 277–289.
22. Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, et al. (2006). "International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors". *Pharmacol. Rev*. 58 (4): 726—41.
23. Berger J, Moller DE (2002). "The mechanisms of action of PPARs". *Annu. Rev. Med*. 53: 409—35.
24. Kim S-H, Kim S-H, Kim Y-B, Jeon Y-T, Lee S-C, (2009). Genistein inhibits cell growth by modulating various mitogen-activated protein kinases and AKT in cervical cancer cells. *Ann N Y Acad Sci*; 1171: 495–500.
25. Park CE, Yun H, Lee EB, Min BI, Bae H, et al. (2010). The antioxidant effects of genistein are associated with AMP-activated protein kinase activation and PTEN induction in prostate cancer cells. *J Med Food;* 13: 815–820.
26. Schröder C., Matthies A., Engst W., Blaut M., Braune A. (2013). Identification and expression of genes involved in the conversion of daidzein and genistein by the equol-forming bacterium Slackia isoflavoniconvertens. *Appl. Environ. Microbiol*; 79:3494–3502.
27. Marrian G.F., Haslewood G.A. (1932). Equol, a new inactive phenol isolated from the ketohydroxyoestrin fraction of mares' urine. *Biochem. J*; 26:1227–1232.
28. Shutt D.A., Braden A.W.H. (1968). The significance of equol in relation to the estrogenic responses in sheep ingesting clover with a high formononetin content. *Aust. J. Agric. Res*; 19:545–553.
29. Guadamuro L., Dohrmann A.B., Tebbe C.C., Mayo B., Delgado S. (2017). Bacterial communities and metabolic activity of faecal cultures from equol producer and non-producer menopausal women under treatment with soy isoflavones. *BMC Microbiol*; 17:93.
30. Kawada Y., Yokoyama S., Yanase E., Niwa T., Suzuki T. (2016). The production of S-equol from daidzein is associated with a cluster of three genes in Eggerthella sp. YY7918. *Biosci. Microbiota Food Health*; 35:113–121.
31. Kilkkinen A., Stumpf K., Pietinen P., Valsta L.M., Tapanainen H., et al. (2001). Determinants of serum enterolactone concentration. *Am. J. Clin. Nutr*; 73:1094–1100.
32. Clavel T., Henderson G., Alpert C.A., Philippe C., Rigottier-Gois L., et al. (2005). Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. *Appl. Environ. Microbiol*; 71:6077–6085.
33. Jefferson W.N. (2010). Adult Ovarian Function Can Be Affected by High Levels of Soy. *J. Nutr*; 140:2322S–2325S.
34. Lord R.S., Bongiovanni B., Bralley J.A. (2002). Estrogen metabolism and the diet-cancer connection: Rationale for

assessing the ratio of urinary hydroxylated estrogen metabolites. *Altern. Med. Rev.*; 7:112–129.

35. Wada K., Nakamura K., Masue T., Sahashi Y., Ando K., et al. (2011). Soy consumption and urinary sex hormone levels in Japanese preschool children. I am. J. ЭпидемиолEpidemiol ; 173 :998-1003.
36. Todaka E., Sakurai K., Fukata H., Miyagawa H., Uzuki M., et al. (2005). The effect of phytoestrogens on the fetus. Difference in phytoestrogen status between mother and fetus. *Environment. Res*; 99: 195-203.
37. Maskarinets G., Morimoto Yu., Novotny R., Nordt F. J., Stanczyk F. Z., et al. (2005). Urinary levels of sex steroid excretion during soy exposure among young girls: a pilot study. *Nutr. Rak*; 52 :22-28.
38. Sirotkin AV, Harrath AH. (2014). Phytoestrogens and their effects. *European journal of pharmacology*; 741:230–6.
39. Nagata S., Inaba S., Kawakami N., Kakizo T., Shimizu H. (2000). Feedback of soy product consumption with serum androgen and estrogen concentrations in Japanese men. *Nutr. Rak*; 36 :14-18.
40. Tanaka M., Fujimoto K., Chihara Y., Torimoto K., Yoneda T., et al. (2009). Isoflavone supplementation stimulated the production of serum equol and reduced serum dihydrotestosterone levels in healthy male volunteers. *Prostate cancer*; 12: 247-252.
41. Applegate K. S., Rawls J. L., Ranard K. M., Chon S., Erdman J.V. Soy consumption and prostate cancer risk: an updated systematic review and meta-analysis. *Nutrients.*; 10: 40.
42. Huzer S., Gut S., Jost H. G., Soukup S. T., Kerle J., et al. (2018). Effect of isoflavones on human breast tissue and thyroid hormones: a comprehensive safety assessment. *Arch. Toxicol*; 92: 2703-2748.
43. Messina M., Redmond G. (2006). Effect of soy protein and изофлавоновsoy isoflavones on thyroid function in healthy adults and patients with hypothyroidism: a review of the relevant literature. *Thyroid gland*; 16: 249-258.
44. Satyapalan T., Manuchehri A.M., Thatcher N. J., Rigby A. S., Chapman T., et al. (2011). Effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized double-blind study. cross-sectional study. *J. Klin. Endocrinol. Anew one*; 96: 1442-1449.
45. Li J., Teng S., Wang V., Chen Yu., Yu S., et al. (2011). Effect of soy consumption with food on maternal thyroid function and serum levels of thyroperoxidase antibodies in early pregnancy. *J. Med. Food.*; 14: 543-550.
46. Konrad S. S., Chiu H., Silverman B. L. (2004). Soy formula complicates the treatment of congenital hypothyroidism. *Arch. Dis. Child*; 89: 37-40.
47. Konrad S. S., Chiu H., Silverman B. L. (2004). Soy formula complicates the treatment of congenital hypothyroidism. *Arch. Dis. Child*; 89: 37-40.
48. Zung A., Shachar S., Zadik Z., Kerem Z. (2010). Treatment изофлавонамиwith soy-derived isoflavones in children with hypercholesterolemia: *a pilot study. Zh. Pediatrician. Endocrinol. Anew one*; 23 :133-141.