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A potential treatment with phytoestrogens: A literature review of experimental models on female rat's reproductive health

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Abstract

Introduction: Phytoestrogens are nonsteroidal substances produced from plants with biological properties such as estrogen. The two main types of phytoestrogens are flavonoids and non-flavonoids. Flavonoids, including isoflavones, are among the most estrogenic compounds, and due to their structural similarities, they can bind to estrogen receptors. Isoflavones have been found in various foods, including fruits, vegetables, sprouts, seeds, and oilseeds (including flaxseeds). This review focuses on plants phytoestrogens that contain flavonoids, isoflavones, daidzein, and genistein. In addition, isoflavones can also be considered endocrine disruptors with the possibility of negative effects on the state of health in certain parts of the population or environment. This literature review will include phytoestrogen-rich crop yields on the reproductive health of mice.

Method Systematic review: Literature searches are conducted on databases such as PubMed, ScienceDirect, Google Scholar, and Cochrane, with time limits. From 2014 to 2024, searches were carried out on this database, considering studies involving herbs, phytoestrogens, isoflavones, and genistein in ovariectomy rat's model (OVX). The study found that plants rich in phytoestrogens can overcome post-ovariectomy complaints, increase estrogen levels, and increase normal cell proliferation. This herb is used as an effective alternative therapy in treating post-ovariectomy complaints.

Result: The search results found 2,401 studies on phytoestrogens and hypoestrogenics in the reproductive organs.

Conclusion: Phytoestrogens have active compounds that can improve the reproductive system after ovariectomy in female mice.

Keywords: OVX; Isoflavones; Genistein; Phytoestrogen

1. Introduction

Phytoestrogens are compounds derived from plants or plant materials whose structure resembles 17β-estradiol and have estrogenic effects. Isolevon, stilbene, coumestan, and lignans are four phenolic chemicals that fall under the category of phytoestrogens. Flavonoids including isoflavones, coumestans, and prenyl flavonoids, and non-flavonoids

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including lignans, are among the most estrogenic compounds, and due to their structural similarities, they can bind to estrogen receptors. These substances are found in a variety of foods such as fruits, vegetables, beans, and whole grains. The subgroups of isoflavones that include their glycosides are daidzein, genistein, biochanin A, glicentetine, and formononetin. Lignans found in mammals include secoisolariciresinol, syringaresinol, matairesinol, lariciresinol, pinoresinol, 7-hydroxy matairesinol and arctigenin (Poluzzi et al. 2014) (Sirotkin et al. 2017). This review focuses on plants in the form of phytoestrogens containing flavonoids, isoflavones, daidzein, and genistein in ovarian model mice. When consumed, they exert estrogenic and/or antiestrogenic effects. Isoflavones are considered chemoprotective and can be used as an alternative therapy for a variety of hormonal disorders, including some types of cancer or menopausal symptoms(Setyarini, A.I., Wiyasa, I.W.A, Ratnawati, R., Indrawan 2019)

This phytoestrogen is often consumed by humans, especially by women who are experiencing perimenopause or menopause, because it is believed to have a positive effect on the body that lacks the hormone estrogen. Phytoestrogens are also used to reduce menopausal symptoms and increase fertility in reproductive women who experience reproductive disorders (Rusnaidi et al. 2022). Isoflavones have been found to act as antagonists or as agonists to endogenous estrogens. Endogenous estrogen regulates the estrus cycle through the influence of prostaglandin synthesis (Puranik et al. 2019). Endogenous estrogen along with its receptors, namely estrogen receptors (ER), have two subtypes, ERα and ERβ. ERα is mainly present in female reproductive organs such as mammary glands and the uterus, whereas ERβ is found throughout the body regardless of gender. The ERβ gene was cloned in 1996, and the receptor is known to be involved in several diseases such as osteoporosis, breast cancer, and obesity, although many functions are still unclear (Nanashima et al. 2018)

Estrogen has both reproductive and brain functions and acts on the central nervous system through the transduction of complex signals involving estrogen receptors (ER). The biological effects of estrogen reach cells through the modulation of alpha ER and beta ER which are ligand-activated transcription factors in most cells. Alpha ER and beta ER mostly accumulate in the central nervous system including the hippocampal synapses and prefrontal cortex. The classical genomic effects of estrogen involve organs as signaling compounds that bind to and activate alpha ER and beta ER in cells, then act as transcription factors for genes containing estrogen response elements (ERE). ER alpha and ER beta bind to ERE with similar specificity and affinity according to the sequence of DNA-binding domains (Martinez et al. 2023). Estrogen is mostly produced by the ovaries, especially 17β-estradiol (E2), and controls several biological processes, such as growth, proliferation, and cell (Yusharyahya et al. 2020). Phytoestrogens can bind with estrogen receptors (ERα and ERβ), albeit with a lower affinity than estradiol (E2), thereby inducing biologically detectable effects. In addition, they can inhibit the binding of sexual steroids to proteins and can compete with E2 to bind to both RE subtypes present in the target reproductive organs. E2 is a female sex steroid hormone that is synthesized primarily by follicle cells in the ovaries. It plays a key role in the regulation of the female reproductive process. Along with progesterone, it promotes lordosis behavior that acts on ERα in the hypothalamic Ventromedial Nucleus (VMN) (Sergio et al. 2019). Estradiol (E2) also induces uterine epithelial cell proliferation and is essential for the maintenance of normal epithelial morphogenesis, cytodifferentiation, and secretory activity. The mitogenic response of uterine epithelial cells to the effects of E2 is mediated primarily by ERα which exhibits cyclic variation during the estrus cycle. In the vagina of rodents, E2 promotes vaginal epithelial proliferation and cytodifferentiation. Although ERα and ERβ are present in vaginal epithelial cells, E2-induced proliferation, cornification, and normal epithelial stratification are mediated by ERα (Li et al. 2016) (Sergio et al. 2019). The use of exogenous estrogens in place of endogenous estrogens in hormone replacement therapy (HRT) will be discussed in this article. This study will look at how phytoestrogens from various plant sources can affect the reproductive system in female mice model ovariectomy.

2. Methods

This systematic review was conducted to determine the association between herbal plants and their phytoestrogen content, which can increase estrogen levels in cases of hypoestrogenism. The following databases were searched using Google Scholar, ScienceDirect, PubMed, and Cochrane. The following Medical Subject Heading (MeSH) terms were entered individually or in combination in the search: “Herb” and “Phytoestrogen” and “” and “OVX” and “Hypoestrogen” reproductive journals. For this evaluation, all selected article publications that met the inclusion criteria, namely articles with publication years 2014–2024, were placed and evaluated.

3. Results

The search results found 2,401 studies on phytoestrogens and hypoestrogens" in reproductive organs. Then based on the inclusion criteria, we found the 10 most relevant research articles to the topic of discussion.

No	Title	Bioactive compounds	Research sample	Induction of hypoestrogenic (Rats model)	Treatment	Outcome	References
1.	Effects Of Phytoestrogens Red Bean Extract (*Phaseolus vulgaris* L.*)* Against Estradiol Levels, Vaginal Mucosal Epithelial Thickness, Endometrial Thickness and Femoral Bone Osteoclasts of Menopausal Rats	Isoflavones	24 female *Wistar* rats	Ovariectomy	The samples were divided into 6 groups: control rat group, ovariectomy rat group with no treatment, ovariectomy rat group and given estradiol tablets 60µg/200gBW, ovariectomy rat group given red bean extract dose I (35mg/200gBW), ovariectomy rat group and given red bean extract dose II (70mg/200gBW), and ovariectomy rat group and given red bean extract dose III (140mg/200gBW).	Red bean extract can raise endometrial thickness, raise vaginal mucosal epithelial thickness, raise estradiol levels, and stop the growth of osteoclast cells in the femur bone.	Andriani *et al.,* 2024 (Andriani et al. 2024)
2	Influence of genistein and diadizine on regularity of estrous cycle in cyclic female *Wistar* rat: interaction with estradiol receptors and vascular endothelial growth factor	Genistein and diadizine	40 female *Wistar* rats	Diet control	The samples were divided into 2 groups: the control group that fed a casein-based diet and the isoflavones group that fed a casein-based diet and gavaged 50 mg/kg/day soy isoflavones extract 40%.	The irregularity of the estrous cycle caused by isoflavones was observed in ovarian and uterine tissues through changed and increased expression of VEGF, ERβ, and ERα.	Elsayed *et al.,* 2022 (Elsayed et al. 2022b)
3	Impact of Soybean Phytoestrogen-Rich Extract on Hormonal Imbalance and Ovarian Function in Menopausal Rat Induced with 4-Vinylcyclohexene Diepoxide: A Neglected Naturaceutical	Isoflavonoids	30 female albino *Wistar* rats	Ovariectomy	The samples were divided into 3 groups that were induced with 80 mg/kg of 4-vinylcyclohexene dioxide. The rats were then treated with either standard estradiol therapy (14 ug/kg) or different	When it comes to managing hormonal imbalance and ovarian function, high-dose soybean phytoestrogen-rich extract therapy seems to be a more successful option than hormone replacement therapy.	Olawale *et al.,* 2024 (Olawale et al. 2024a)

					concentrations of the phytoestrogen-rich soybean extract (200 mg/kg, 400 mg/kg, and 600 mg/kg).		
4	Estrogenic and Antioxidant Activities of *Pterocarpus soyauxii* (Fabaceae) Heartwood Aqueous Extract in Bilateral Oophorectomized Wistar Rat	Flavonoids, polyphenols, and tannins	35 female albino *Wistar* rats	Oophorectomy	The samples were divided into 7 groups: OVX group, sham group, and 5 treatment groups with -*e aqueous* extract of *Pterocarpus soyauxii* heartwood at doses of 50, 100, 200, 300, and 400 mg/kg and *estradiol valerate* (E2V) at a dose of 1 mg/kg.	*P. soyauxii aqueous* extract demonstrates estrogenic and antioxidant effects that can prevent postmenopausal symptoms by improving lipid profile and insulin sensitivity, vaginal stratification, and oxidative stress reduction without adverse effects on the endometrium or mammary gland.	Ngadena *et al.,* 2021 (Mengue Ngadena et al. 2021a)
5	Beneficial Effects of Flaxseed and/or Mulberry Extracts Supplementation in Ovariectomized Wistar Rats	Flavonoids, coumarins, chromones, xanthones, phytoalexins, vitamins A, D, E, K, lignans, and secoisolariciresinol diglycoside (SDG)	33 adults female *Wistar* rats	Ovariectomy	The animals were divided into 5 groups and treated with: saline (n = 6), estrogen (n = 6), flaxseed extract (n = 7), mulberry extract (n = 7), and a mixture of flaxseed plus mulberry extract (n = 7).	The advantage of mulberry extract and flaxseed as a substitute is to lessen and/or stop the side effects brought on by low estrogenic action.	Pereira *et al.,* 2022 (Pereira et al. 2022a)
6.	*Nigella sativa* oil (NSO) restores hormonal levels, and endocrine signals among thyroid, ovarian, and uterine tissues of female *Wistar* rats following sodium fluoride toxicity	Isoflavone, genistein and daidzein	28 mature female *Wistar* rats	Ovariectomy	The samples were divided into 4 groups: control group; NaF group, orally received NaF (20 mg/kg b.wt.) daily; NSO/NaF, orally received NSO (300 mg/kg b.wt.) two weeks before being given NaF and continued throughout the experiment; and	Compared to the NaF-treated group, NSO dramatically increased the amounts of antioxidant molecules and decreased lipid peroxidation in the tissues under examination. Comparing the NSO-intoxicated group to the control group, NSO also up-	Elghareeb *et al.,* 2024 (Elghareeb et al. 2024)

					NSO+NaF group orally received NSO concurrently with NaF.	regulated antioxidant enzymes, anti-apoptotic protein, bone morphogenetic protein, zona pellucida sperm-binding protein, and thyroid stimulating hormone; on the other hand, it down-regulates inflammatory cytokines, apoptotic proteins, ERα, ERβ, and thyroid stimulating hormone receptors. Furthermore, NSO lessened tissue damage caused by NaF to the thyroid gland, ovaries, and uterus.	
7.	*Salvia officinalis* mitigates uterus and liver damages induced by an estrogen deficiency in ovariectomized rats	Phenolic, flavonoid, and tannin	Female *Wistar* rats	Ovariectomy	The samples were divided into 4 groups as follows: negative controls, positive controls treated with sage leaves, ovariectomized rats (group OVX), and ovariectomized rats receiving either sage (OVX-S) or hormonal (Group OVX-E) treatments, respectively.	In ovariectomized rats, sage leaves reduce estrogen insufficiency, liver damage, and uterine damage caused by an imbalance in antioxidants. Menopausal women may benefit from its helpful role without adverse effects to affirm its estrogenic potential, maximize its antioxidant capacity, and prevent the primary health issues found after menopause.	Ghorbel *et al.,* 2021 (Koubaa-Ghorbel et al. 2021)
8.	Estrogenic Activity of Mahoni Seed Ethanolic Extract [*Swietenia mahogany* (L.) *Jacq*] on Uterus Weight, Bone	Phenolic compounds, lipids, isoprenoids like sterols, terpenes, carotenoids	30 female rats	Ovariectomy	The samples were divided into 6 groups: normal control, positive control given estradiol dose of 0.18 mg/kg body weight	The results of the study demonstrated that Mahoni Seed Ethanolic Extract could raise the weight of the uterus, the length of the	Hasibuan *et al.,* 2020 (Hasibuan et al. 2020)

	Density and Mamae Gland Proliferation on Ovariectomized Rats	lignans, and secoisolarisiresinol			(BW), negative control given Na-CMC 1%, and group 4, 5, 6 givens Mahoni Seed Ethanolic Extract orally for 14 consecutive days with doses of 50, 100, 200 mg/kg BW.	estrus phase in the estrus cycle, the density of the rats' bones, and the proliferation of their mammae glands. The findings showed that Mahoni Seed Ethanolic Extract has phytoestrogenic effects on rats that had undergone ovariectomy.	
9.	Effects of estrogen deficiency on liver function and uterine development: assessments of *Medicago sativa's* activities as estrogenic, anti-lipidemic, and antioxidant agents using an ovariectomized mouse model	Isoflavonoids, flavonoids, lignans, and commustans	70 female mice	Ovariectomy	The samples were divided into 5 groups: control, treated with Medicago sativa (0.75 g/kg/day), ovariectomized, ovariectomized treated with β-estradiol (1 µg/day), or with *Medicago sativa*.	Lipid peroxidation, antioxidant enzyme activity, and lipid balance are all improved by M*edicago sativa* treatment. This is most likely caused by the plant's abundance of flavonoids and polyphenols, which are known to be phytoestrogenic and antioxidant compounds.	Jdidi *et al.,* 2021 (Jdidi et al. 2021)
10.	Identification of the Active Ingredient and Beneficial Effects of *Vitex rotundifolia* Fruits on Menopausal Symptoms in Ovariectomized Rats	Flavonoids	36 female *Sprague-Dawley* rats	Ovariectomy	The samples were divided into 4 groups: sham, ovariectomy, ovariectomy treated with 100 mg/kg *Feramin Q* (FeQ) suspension in 0.5% *methylcellulose* (MC), and ovariectomy treated with *Vitex rotundifolia* Fruits (VFE) group were orally treated with 50 mg/kg VFE in 0.5% MC.	The improvement of uterine atrophy, rise in blood estradiol and ER expression, and reduction of body weight gain in animal trials all supported the estrogen-like activity of VFE. As a result, the ability of *V. rotundifolia* to alleviate menopausal symptoms was validated, and the active components' mode of action in ER was disclosed.	Lee *et al.,* 2021 (Lee et al. 2021)

Many herbs, especially those connected to the reproductive organs, have been shown to work well as a substitute for hypoestrogen therapy, according to the research paper. Table 1 displays the attributes of the obtained research articles.

4. Discussion

4.1. Herbal Plants as Phytoestrogens

Natural substances called phytoestrogens are found in a wide variety of plants and foods, including soy, dairy, flaxseeds, and hops. The chemical structures of these substances are comparable to those of estrogen (Canivenc-Lavier and Bennetau-Pelissero 2023). For every person, though in greater quantities in women, estrogen is a necessary hormone for good health. In addition to regulating metabolism and promoting reproduction, it keeps bones healthy (Ceccarelli et al. 2022). Due to their potential physiological similarities to estrogen, phytoestrogens may be beneficial to individuals experiencing reduced levels of estrogen, such as those going through menopause. It's crucial to remember that for phytoestrogens to have any discernible impact on the body, a person must regularly consume very large amounts of them (Rowe and Baber 2021).

Phytoestrogens are substances that are present in over 300 plants naturally. They mimic the actions of the hormone estrogen, which is involved in numerous bodily processes (Patra et al. 2023). Estrogen affects libido, menstruation, and sexual development in females. Estrogen regulates bone strength, cognitive function, and the metabolism of fats and carbohydrates in both sexes. Therefore, it's critical to have enough estrogen in your body. Because of their close resemblance to estradiol in terms of chemical structure, phytoestrogens mimic estrogen. The body makes this kind of estrogen (Petrine and Del Bianco-Borges 2021). According to studies conducted by Andriani et al. in 2024, Phytoestrogens bind to estrogen receptors, promote cell proliferation, and affect the expression of growth factors and other regulatory proteins to produce effects on reproductive organs and bones like those of estrogen. By partially reestablishing the hormonal equilibrium disturbed by reduced endogenous estrogen levels, these effects can help alleviate menopausal symptoms like osteoporosis and vaginal shrinkage (Andriani et al. 2024). Isoflavones are phytoestrogens that can interact with estrogen receptors (ERs) in a variety of tissues, including reproductive organs. Examples of these phytoestrogens are genistein and daidzein. The administration of isoflavones to female Wistar rats resulted in a considerable rise in ovarian and uterine weights, which were related to endometrial proliferation and hyperplasia, as revealed by the study conducted by Elsayed et al. in 2022. The estrous cycle in female rats was similarly impacted by isoflavones, resulting in abnormalities an extension of the estrus phase, and a reduction in the diestrus phase (Elsayed et al. 2022).

4.2. Mechanism of phytoestrogen

Estrogen receptors (ER) in mammals, ERα and ERβ, regulate various biological processes such as cell growth, survival, and differentiation. These proteins belong to the nuclear receptor family and have unique structural and functional domains. ER subtypes are derived from two different genes and exhibit different patterns of expression. Selective ER modulators (SERMs) are molecules that exhibit agonistic or antagonistic actions based on the ER subtype. ER-alpha (ERα) influences cell division, while ER-beta (ERβ) controls cell death. Selective ER modulators (SERMs) are isoflavone-based molecules that favor ERβ. ERα is more sensitive to endogenous estrogen (estradiol), while ERβ is more sensitive to exogenous estrogen from natural sources like phytoestrogens. Extra estrogen receptors are not dependent on low levels of estrogen, and enough phytoestrogens can attach to unbound estrogen receptors, raising estrogen levels and impacting fertility returns, endometrial cell proliferation, and endothelial number and function, which helps maintain blood vessel form and function (Lecomte et al. 2017)

Phytoestrogens, particularly isoflavones like genistein and daidzein, manage hormonal balance in hypoestrogenic situations like menopause by imitating estrogen and controlling estrogen levels. They also have anti-inflammatory and antioxidant properties, reducing oxidative stress and inflammation. Phytoestrogens also influence hormone synthesis and release, regulating the hypothalamic-pituitary-gonadal axis. They contribute to maintaining ovarian reserve and reproductive health, making them a promising natural substitute for managing menopausal symptoms (Olawale et al. 2024).

The study assessed *Pterocarpus soyauxii* heartwood extract's estrogenic and antioxidant properties in *Wistar* rats that had had their ovaries removed. The extract led to increased uterine weight, protein levels, and epithelial thickness, as well as vaginal cornification, according to the results. By inhibiting 1,1-diphenyl-2-picrylhydrazyl (DPPH) and ethylbenzothiazoline-6- sulfonic acid (ABTS) free radicals, it also demonstrated antioxidant potential, which was connected to flavonoids and phenolic substances. The extract was found to be beneficial in treating postmenopausal cardiovascular diseases, lowering body weight, insulin resistance, dyslipidemia, and abdominal fat in an 84-day model.

According to this data, *P. soyauxii* extract may help postmenopausal women with hypoestrogenism-related issues without changing their risk of developing estrogen-dependent cancer (Mengue Ngadena et al. 2021).

Phytoestrogens, non-steroidal compounds found in plants like flaxseed and mulberry, mimic or modulate estrogenic actions in the body by binding to estrogen receptors. They can elicit both estrogenic and anti-estrogenic effects, depending on the concentration of endogenous estrogens and tissue type. In the absence of endogenous estrogen, phytoestrogens can activate estrogen receptors, leading to increased endometrial thickness, improved lipid profiles, and enhanced pituitary weight. Their high phenolic content contributes to their antioxidant properties, including protection against cardiovascular diseases and reduced oxidative stress (Pereira et al. 2022)

5. Conclusion

Biological characteristics are present in phytoestrogens with a range of medicinal effects. It works similarly to endogenous estrogens and has been demonstrated to help postmenopausal women with a range of health issues as well as menopausal symptoms. Because of their structural resemblance to estrogen, phytoestrogens, which are based on the nuclear ring system, have bioactivity. They have structural and functional similarities with endometrial and ovarian estrogen, both of which are crucial to the female reproductive process. A range of dietary supplements and hormone replacement treatments contain phytoestrogens as a substitute for synthetic hormone replacement. Although they are unclear, the risks associated with eating phytoestrogens ought to be a major focus of future research. We may infer that the administration of phytoestrogens to rat test animals has specific physiological effects on the reproductive organs based on the information currently available in this study.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares that there is no conflict of interest in the publication of this article.

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