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REVIEW

Effects of phytoestrogens on reproductive organ health

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Abstract Phytoestrogens are non-steroidal, polyphenolic compounds that are derived from plants and have biological properties similar to those of human estrogens. Their bioactivity, which is based on the core ring system, is caused by their structural resemblance to estrogen. Flavonoids, coumestans, lignans, and stilbenes are the four major categories into which they can be divided. They are structurally and functionally related to ovarian and placental estrogens, which are essential in female reproductive processes. Phytoestrogens are present in numerous dietary supplements and find application in hormone replacement therapy as an alternative to synthetic hormones. In addition, they provide health benefits for osteoporosis, heart disease, breast cancer, and prostate cancer. There is a growing interest in using phytoestrogen as preventative medicine in the form of nutraceuticals. This literature provides comprehensive information about the types, sources, and biological actions of phytoestrogens in the reproductive system.

Keywords Phytoestrogen · Genistein · Isoflavones · Breast cancer · PCOD

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Introduction

Phytoestrogens are non-steroidal polyphenolic plant-derived compounds that can exert an estrogenic and/or antiestrogenic effect in mammals. They are referred to as "dietary estrogens" because they are structurally and functionally similar to the endogenous (17-β estradiol) estrogen found in animals (Petrine and Bianco-Borges 2021). Phytoestrogens belong to a large group of substituted phenolic compounds known as polyphenols that are widely distributed in the plant kingdom. Although the classification of phytoestrogens is still unclear and vague, broadly they can be divided into four major classes based on their basic chemical structure: flavonoids (flavonols, isoflavones, and prenylflavonoids), lignans, coumestans and stilbenes as depicted in Fig. 1 (Poluzzi et al. 2013; Sirotkin and Harrath 2014). Phytoestrogens are distributed in more than 300 plant species, predominantly in Leguminosae, subfamily Papilionoidea. They are frequently found in various plant sources, including herbs, grains, vegetables, and fruits, as shown in Table 1 (Panche et al. 2016; Watson et al. 2018; Anandhi Senthilkumar et al. 2018).

Phytoestrogens have a molecular structure similar to endogenous estrogen and estradiol, as shown in Fig. 2. The propensity of these phytoestrogens to bind to estrogen receptors in different cell types and produce estrogenic or antiestrogenic actions is due to their structural similarity with their endogenous counterparts (Martin et al. 1978; Bacciottini et al. 2007). Phytoestrogens, known as dietary estrogens, benefit all mammals, including humans. They are non-steroidal plant compounds that undergo metabolism to produce compounds structurally and functionally related to ovarian and placental estrogens (Desmawati and Sulastri 2019). They play a significant role in facilitating the rebalance of hormones in women during menopause. Hormone replacement therapy as an alternative to synthetic hormones

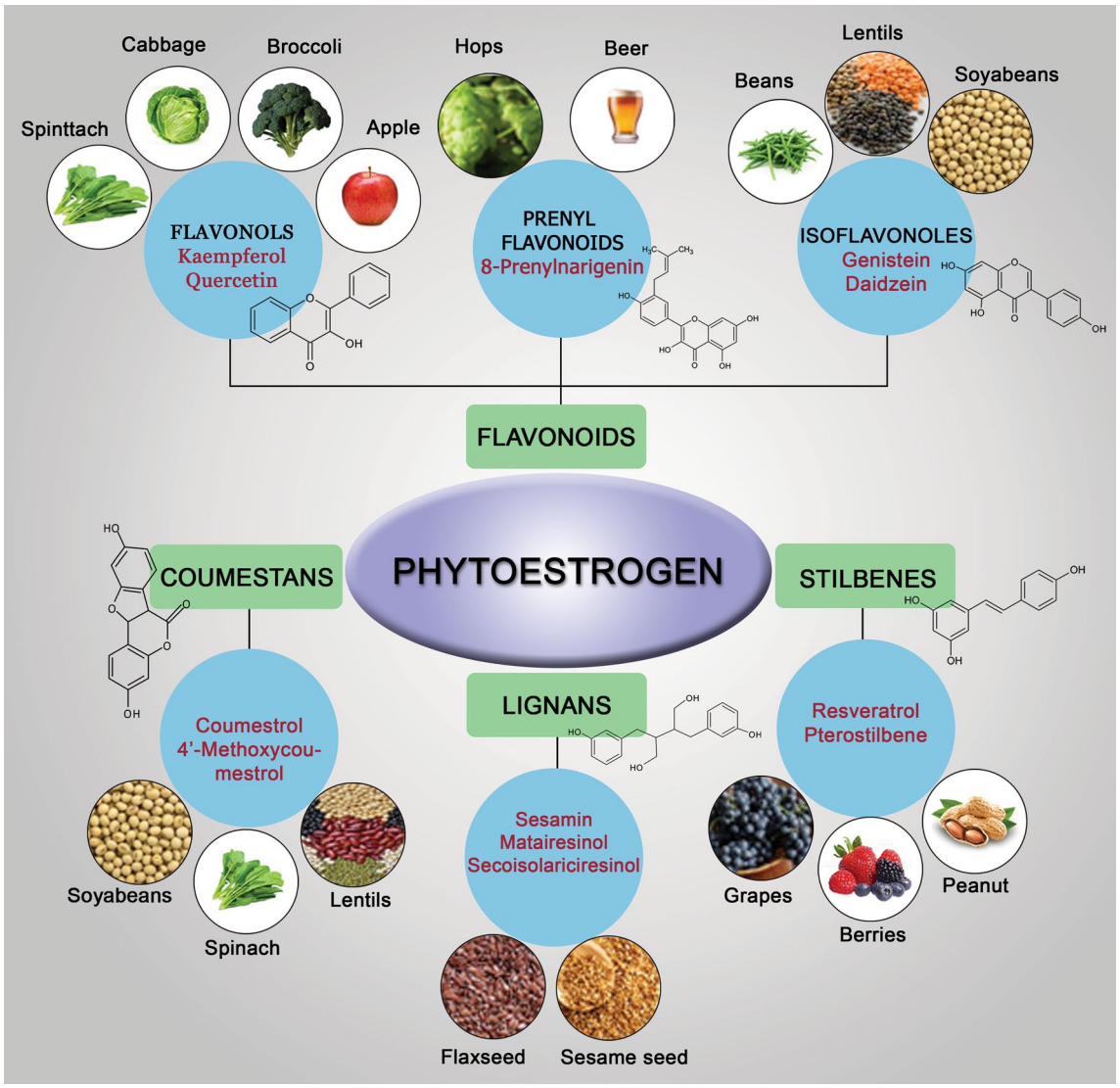

Fig. 1 Classification of phytoestrogen with examples

Table 1 Sources of phytoestrogens

Phytoestrogen	Sources
Flavonoids	Red clover, soyabeans, lentils, legumes, kudzu
Isoflavones	Cabbage, spinach, apple, red wine, grapes, onions, tea, broccoli, strawberries, beans, tomato
Flavanols	Hops, beers
Prenyl flavonoids	
Lignans	Flaxseed, pumpkin, garlic, apricot, alfalfa, sunflower seeds, broccoli, cabbage, dates, kudzu, brussel sprout, coffee, oats
Coumestans	Alfalfa, spinach, soya sprouts, mung bean, red clover
Stilbenes	Grapes, peanuts, wine, soy, strawberries, mulberries cranberries, blueberries

is therefore a potential application of these phytoestrogens (Rietjens et al. 2017). They can show agonist and antagonist activity on reproductive organs and the brain pituitary gonad axis (hypothalamus). Other than benefits, there are certain risks associated with phytoestrogen consumption. A clinical study demonstrated that women experienced secondary infertility due to continuous soy intake for 14 years (Gore et al. 2015). Evidences from animal studies also show that

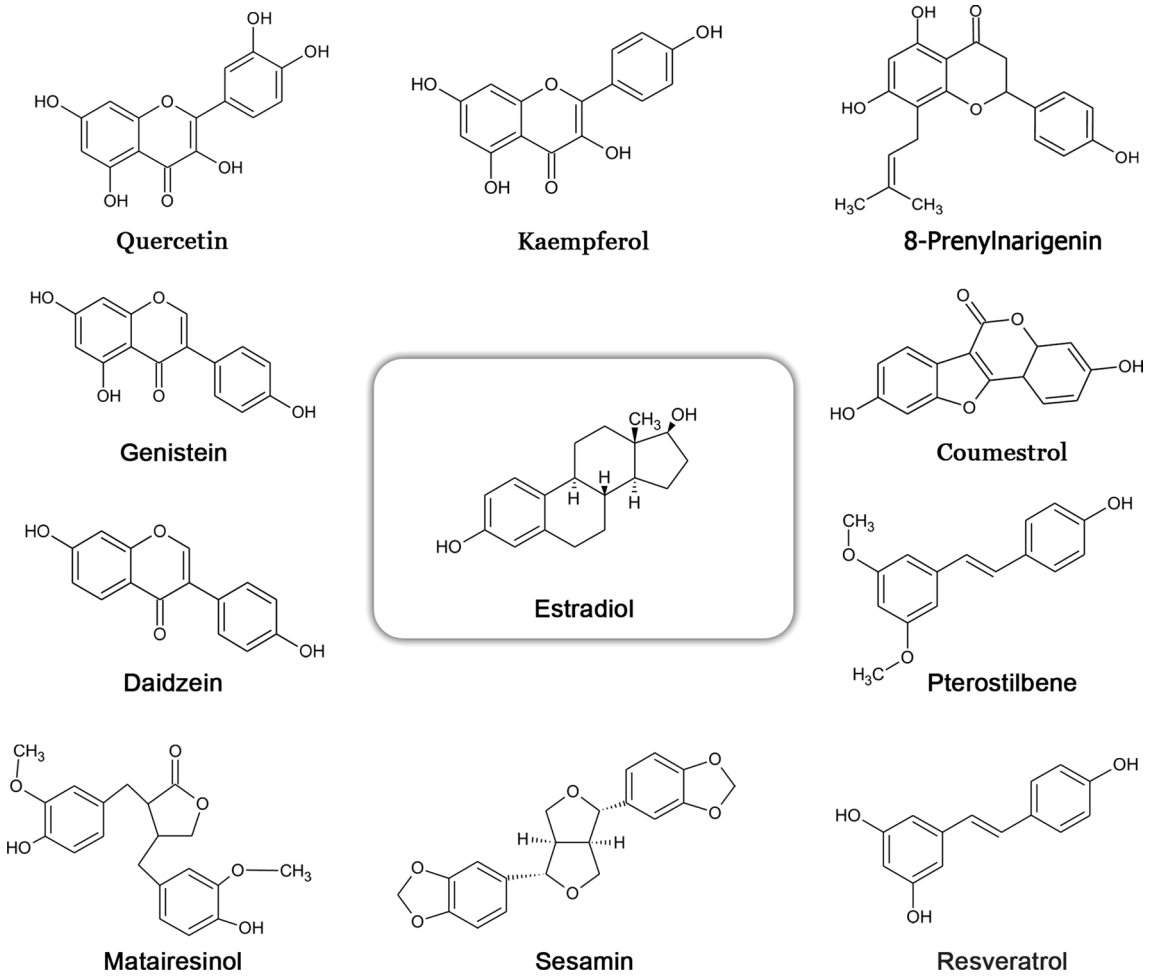

Fig. 2 Chemical structure of estradiol and major phytoestrogens

phytoestrogens can disrupt the endogenous hormone level, ovulatory cycle behavior, and endocrine disruption during the developmental stage (Mahalingam et al. 2016). The present review provides a mechanistic insight into the biological activities of phytoestrogens in the mammalian reproductive system and related cancer through interaction with estrogen receptors. The article also highlights the benefit of phytoestrogen-containing food in improving the symptoms and complications of estrogen deficiency in postmenopausal women.

Mechanism of action of phytoestrogens

Phytoestrogens have been linked to a broad spectrum of biochemical effects. They are low molecular weight compounds that chemically mimic endogenous estrogen in that they have a phenolic ring with multiple hydroxyl groups. Because of this structural similarity, they can bind to estrogen receptors and provide either an estrogenic or an antiestrogenic action. Non-receptor mediated effects include the antioxidant effect, inhibition of enzymes involved in the synthesis of oestradiol, and steroids such as 17-hydroxysteroid dehydrogenase, 5cz-reductase, or aromatase, and suppressing kinases (Desmawati and Sulastri 2019). The intracellular mechanism of action of phytoestrogens includes (Nynca et al. 2009; Lecomte et al. 2017; Domínguez-López et al. 2020):

1. Effect on ER-α, ER-β, and other nuclear receptors like progesterone, androgen, or aryl hydrocarbon receptors
2. Enzyme inhibition (Steroidogenesis)
3. Inhibition of DNA topoisomerase (I and II)
4. Antioxidant activity
5. Inhibition of tyrosine kinase
6. Stimulation of sex hormone-binding globulin

Even though phytoestrogens can bind to both α and β-estrogenic receptors, they have more affinity toward β-receptors. They attach to β-receptors and act as agonists, partial agonists, and antagonists (Mottaghi and Abbaszadeh 2022). In vitro studies demonstrate that phytoestrogens

bind with the estrogen receptor more efficiently than other functioning domains (Lecomte et al. 2017). In experiments utilizing the pure protein, isoflavonoids exhibit a surprisingly high affinity for the estrogen receptor. Still, they are poor competitors in whole-cell or cytosolic preparations, perhaps due to interactions with binding proteins (Akiyama et al. 1987). Phytoestrogens can also act by non-estrogen receptor-mediated mechanisms to exert their biological effects by inhibiting the activity of several enzymes (like protein tyrosine kinases, DNA topoisomerase I, DNA topoisomerase II, and ribosomal S6 kinase), which are involved in cell-signalling mechanisms and nuclear events like cell proliferation and cell division (Markovits et al. 1989; Sunita and Pattanayak 2011). The newly discovered estrogen receptor variant ER appears to have more excellent selectivity for coumestrol and genistein than the conventional estrogen receptor. In comparison to ER-α, coumestrol binds to ER-β twice as strongly, while genistein has a 40-fold greater affinity for ER-β. Dimerization of binding receptors is necessary for transcriptional regulation since cells can express both ER-α and ER- β (Paterni et al. 2014; Kim 2021).

The phytoestrogens act on the peroxisome proliferator-activated receptors (PPAR) ligand, GPER1, estrogen-related receptors, and aryl hydrocarbon receptors. Phytoestrogens can change epigenetic marks and directly modify signaling pathways by affecting the activities of DNA and histone methyltransferases, NAD-dependent histone deacetylases, and other chromatin structure modifiers (Russo et al. 2017). Estradiol synthesis by aromatase can be competitively inhibited by phytoestrogens, which can reduce endogenous estrogen levels. The phytoestrogens add to the complexity of their effects when administered in an "in vivo model" as mixtures of various dietary components that can activate many signaling pathways or affect the same pathways in opposing directions (Jodynis-Liebert and Kujawska 2020). Figure 3 depicts the effect of phytoestrogens on human reproductive health and the underlying mechanisms.

Effect of phytoestrogens on brain pituitary gonad axis

The gonadal axis of the pituitary gland controls mammalian reproduction and releases hormones like gonadotropin-releasing hormone (GnRH) dopamine, and aminobutyric acid. The main gonadotropin hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH), stimulate the production of sex hormones, including estrogen and testosterone, which regulate ovulation in females and spermatogenesis in males (Medigović et al. 2015). Other than activating the function of reproductive organs, estrogens also show feedback effects (positive and negative) via estrogen receptor interaction on the synthesis and secretion of gonadotropin (Kayo et al. 2019).

Since the structure of phytoestrogens is similar to estrogen, it acts as an estrogen inhibitor. GnRH is one of the crucial hormones which has a central function in reproduction. The phytoestrogen flavanone-8-prenylnaringenin inhibits

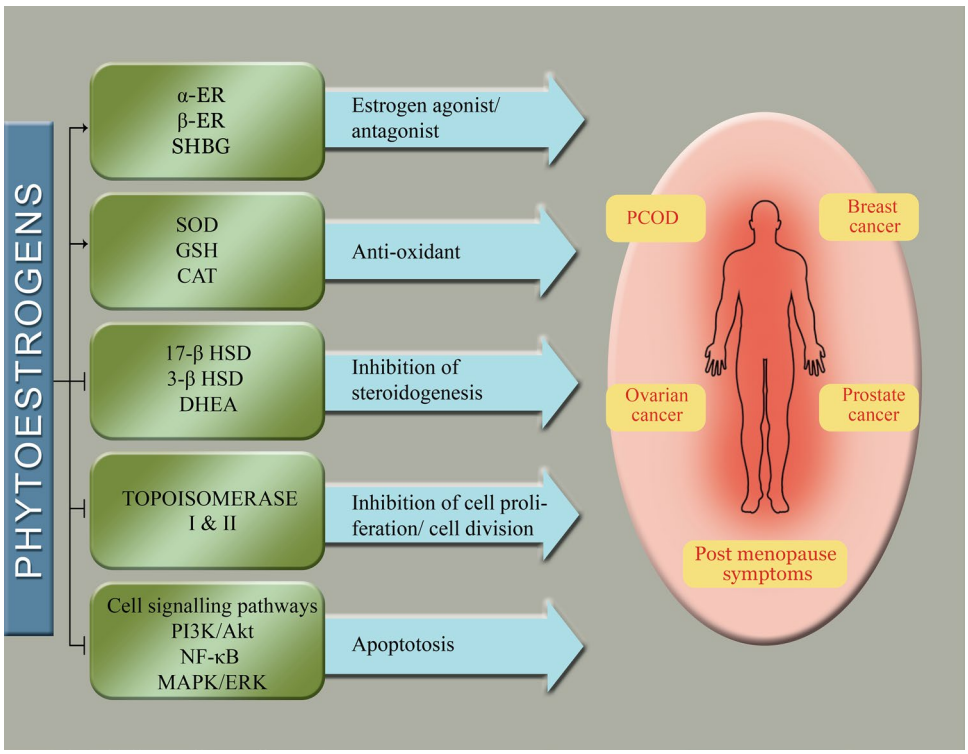

Fig. 3 Effect of phytoestrogens on human reproductive health and the underlying mechanisms

the GnRH through a negative feedback system (Christoffel et al. 2006; Pohjanvirta and Nasri 2022). The phytoestrogen coumestrol inhibits the gene expression of GnRH neurons by binding to the ER receptor and has an inhibitory effect on the reproductive system (Bowe et al. 2003). Coumestrol also inhibits the release of LH by blocking the action of estrogen in the neuroendocrine system. Decreased LH can benefit menopausal women, according to several clinical trials. (Jacob et al. 2001). In mouse hypothalamic GT1-7 neurons, the effect of a high dose of genistein (20 μM) on GnRH release was investigated, and it showed significant enhancement in GnRH secretion by 122.4% in comparison to the control. According to the mechanistic investigation, genistein therapy may have an impact on GnRH secretion by altering the function of kisspeptin receptors, SIRT1, PKCγ and MKRN3 in GT1-7 cells (Xiong et al. 2022).

Effect of phytoestrogens on the male reproductive system

The effects of phytoestrogens on testis have been demonstrated in some preclinical studies. Both coumestrol and genistein decreased gonadotropin-induced testosterone synthesis by cultured Leydig cells. Additionally, genistein was shown to have an inhibitory effect on spermatogenesis and reduces testicular weight (Hedelin et al. 2006; Tran-Guzman et al. 2022).

Effect on prostate cancer

The prostate gland is a convoluted tubule alveolar exocrine gland in mammals. According to studies, a high density of ER receptors on the surface of prostate cancer makes it susceptible to the effects of phytoestrogens (Groot 2006). Enterolactone (mammalian lignans produced from plant lignans by the gut microflora) and genistein were found to play a significant role in reducing the risk of prostate cancer (Azrad et al. 2013; Mottaghi and Abbaszadeh 2022). Shaffie and co workers studied the effect of genestein in cellular signalling targets in PC3 prostate cancer cells. The authors observed that it can reduce metastatic potency by increasing the enzyme activity of caspase-3, and regulating p38MAPK pathways at different transcriptional and protein levels (Shafiee et al. 2022). Soy and rye supplements reduced the tumor volume of prostrate in preclinical animal models (Grammatikopoulou et al. 2020). Regular use of soy, soy products, tofu, legumes, daidzein, genistein, and other plant foods, especially in Asian and Caucasian populations, significantly reduced the risk of prostate cancer. (He et al. 2015; Zhang et al. 2016). The effectiveness of coumestrol, a phytoestrogen present in soybeans and other legumes, against prostate cancer in PC3 and LNCaP cells was reported by Lim and coworkers. The mechanistic study shows that the ERK1/2, JNK MAPK, and PI3K/AKT cell signalling pathways have mainly been implicated in mediating the anticancer effect (Lim et al. 2017).

Genistein effectively protected oxidative stress-related DNA damage in prostate cells, which increased with age and led directly to prostate cancer (Zhao 2011). The cytotoxic activity of enterolactone towards inhibiting tumor cell growth in human prostate carcinoma is attributed to the activation of mitochondria-mediated caspase-dependent apoptotic pathway (Azrad et al. 2013). By modifying blood corticosterone and LH concentrations, Ohno et al. showed that genistein treatment modifies hormone production in the testis and adrenal glands in vivo (Ohno et al. 2003). Growing evidence shows that phytoestrogens, especially lignans and genistein, can modulate the activity/expression of steroidogenic enzymes such as human aromatase, 17β-hydroxysteroid dehydrogenase, and 5α-reductase, which influences the conversion of circulating precursors into active hormones (Kundu et al. 2018; Sirotkin et al. 2021). They also control the disease by antioxidant, anti-angiogenic, and anti-genotoxic activity in different in vitro studies (Desmawati and Sulastri 2019; Torrens-Mas and Roca 2020). Dihydrotestosterone (DHT)-induced proliferation of prostate cancer cell lines is inhibited by resveratrol through the androgen receptor (AR). The chemokine receptor CXCR4, which is increased during cancer metastasis, is likewise inhibited by resveratrol. The presence of AR and CXCR4 antagonists was observed to enhance the effect of resveratrol on the metastatic behaviour of prostate cancer (Jang et al. 2019).

Effect of phytoestrogen on the female reproductive system

Effect on female genital tracts

Phytoestrogens affect both the male and female genital tract. In females, it plays an essential role in the cellular proliferation and hypertrophy of female secondary sexual organs and the proliferation of the endometrium. GnRH neuron receives hormonal and environmental signals from estrogen-responsive kisspeptin neurons (Shughrue et al. 1997; Oakley et al. 2009). These anteroventral periventricular (AVPV) kisspeptin neurons are more in females than males. An experimental study on rats shows that neonatal exposure to genistein decreases the density of neuronal fibers due to the lack of accurate organization of the kisspeptin signaling pathway, which causes a variation in the timing of pubertal onset, irregular estrous cycle, and premature anovulation (Kauffman et al. 2007).

Ovarian, pituitary, and hypothalamus activities of phytoestrogens may change ovarian cycles. Certain plant-derived isoflavonoids may have a direct effect on the ovaries. The phytoestrogens, coumestrol, and genistein bind to ER receptors in granulosa cells. In the early phases of follicular development, phytoestrogens may limit estradiol action, whereas, in the luteal phase, phytoestrogens may augment its effect (Patisaul and Jefferson 2010). The inhibition of follicular development occurs by inhibiting 17-β hydroxysteroid dehydrogenase (17-β HSD) or by inhibiting aromatase enzyme in the ovary (Hong et al. 2008). A preclinical study shows that phytoestrogens have a role in epithelial cell proliferation of the uterus and vagina. Also, the study reported isoflavones induce uterine and pituitary growth in rats (Mc Rodrigues et al. 2018).

Effect on breast cancer

The breast gland is one of the important reproductive organs in females that helps to produce and secrete milk. Many studies show that phytoestrogens play an essential role in the protection from breast cancer. They mainly act by inducing differentiation of breast epithelium during childhood and puberty, thus making the epithelium of the breast less sensitive to carcinogens (Patisaul and Jefferson 2010).

Most breast cancer shows estrogen receptors; hence, estrogen is a tumor growth promoter. The main enzymes involved in estrogen production from androgens and estrone sulfate are aromatase and 17β-HSD. The enzyme aromatase converts the blood androgen into estrone, which is further converted to estrol by 17β-HSD. Also, estrone sulfate (a steroid precursor found in the blood) gets converted to estrone by the enzyme estrogen sulfatase, which is further converted to estrol by 17 β-HSD (Santulli 2013). Phytoestrogens, especially flavones and isoflavones, act as potential agents for preventing cancer by targeting the enzymes aromatase and 17β-HSD as depicted in Fig. 4 (Nakai et al. 2020; Seth et al. 2021). Recent investigations into the mechanisms responsible for the beneficial effects of phytoestrogen have been demonstrated, and it was found that they protect against cancer by regulating various cellular pathways and expression of intracellular protein, as summarized in Table 2.

Recently, few studies showing the effect of phytoestrogens on breast cancer are reported in the literature. It was showed that the ER-β and NF-kB signaling pathways are the two critical targets for genistein. Genistein explicitly targets cells that express ER-β and induces apoptosis by its inhibitory effect on NF-kB, AKT signaling pathway, and HER2 expression (Bhat et al. 2021). In addition, genistein inhibits cancer growth by activating suppressor proteins like BRCA1 and BRCA2 by the overexpression of genes that code for these proteins. In another study, genistein at high concentration was shown to inhibit the proliferation of breast cancer cells (Thangavel et al. 2019). Higher consumption of flaxseed, which is rich in endogenous estrogen is beneficial in lowering the risk of breast cancer (Parikh et al. 2019; Nair et al. 2021).

Effect on polycystic ovarian syndrome (PCOD)

PCOD is an endocrine disorder that arises from a deficiency of aromatase enzyme commonly found in pre-menopausal women. It is clinically described as lacking ovulation, irregularity in the menstrual cycle, polycystic ovaries, and hyperadrenergic properties. PCOD can occur because of several genetic and environmental factors and is usually associated with hyperinsulinemia or insulin resistance. Despite being common among the population, the treatment of this disease

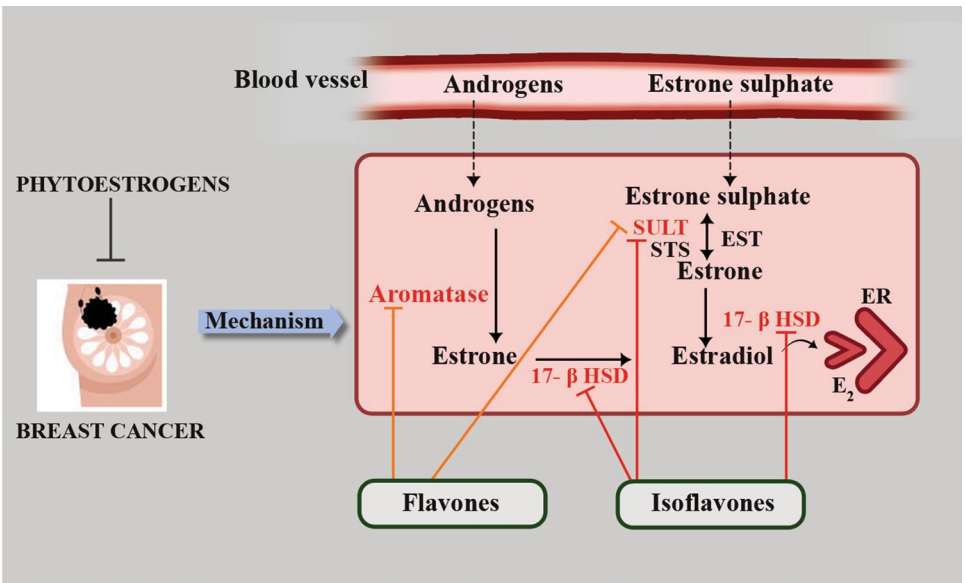

Fig. 4 Mechanism of action of phytoestrogen in breast cancer. Flavones and isoflavones inhibit the enzymes aromatase and 17β-HSD and limit the formation of biologically active estrogens, as well as steroid synthesis in breast cancer cells

Table 2 Summary of the mechanism of action of major phytoestrogens in breast cancer

Phytoestrogens	Mechanism of action	References
Daidzein	AhR-dependent inhibition of CYP1	Choi and Kim (2008)
	Cell cycle arrest at the G1 and G2/M phases by downregulation of cyclin D, CDK2, and CDK4 expression	Choi and Kim (2008)
	Enhances caspase-9 activity indicating cell apoptosis	Dagdemir et al. (2013)
	Apoptosis induced by Fas/FasL apoptosis signaling pathway	Wang et al. (2020)
	Induces apoptosis and inhibits cell division by regulating MEK/ERK 1/2, and PI3K/Akt pathways	Rice and Whitehead (2014), Kaushik et al. (2018)
	Up-regulates the expression/activity of Cyclin D1, p21, p27, p53, p53 and induced cell cycle arrest	Sakamoto et al. (2010)
	Triggers apoptosis by regulating p53/Bax/Bcl-2 signaling pathway	Li et al. (1999)
Genistein	Inhibit DNMT1 and expression of hTERT, reduces estrogenic stimulation in breast cancer	Gong et al. (2003)
	Suppress ER-dependent signal transduction Inhibit ERα mRNA and protein expression	Lee et al. (2014)
	Induce downregulation of E2F1 and CIP2A in breast cancer cell lines, that correlates with growth inhibition and apoptosis	Zhao et al. (2016)
	Suppress cell proliferation by the inhibition of PI3K/Akt-NF-kB pathway	Li et al. (1999), Gong et al. (2003)
	Induce differentiation on mammospheres by regulating PI3K/Akt and MEK/ERK signaling pathways	Liu et al. (2016)
	Promote apoptosis by upregulation of Bax and p21WAF1 expressions Downregulates Bcl-2 and p53 expression	Li et al. (1999)
	Promote apoptosis by downregulation of Bcl-2 and the upregulation of Bax; improves the Bax/Bcl-2 ratio Induces cycle arrest of breast cancer cells via the IGF/PI3 K/Akt pathway	Chen et al. (2015)
	Reduces protein expression of MEK, total ERK, and phosphorylated ERK; inhibits cell growth and facilitates apoptosis	Li et al. (2008)
	Increases EGFR and progesterone receptor expression and controls ER-mediated mammary gland proliferation and differentiation	Cotroneo (2002)
	Block angiogenesis by inhibiting telomerase and DNA topoisomerase	Gong et al. (2003)
	Inhibits cyclin D1 expression and induces cell cycle arrest	Rahal and Simmen (2010)
8-Prenylnaringenin	Suppresses estrogen-signaling through the inhibition of BIG3-PHB2 interactions	Yang et al. (2019)
	modulates the MAPK signaling pathway	Brunelli et al. (2007)
Resveratrol	Inhibits CYP-1A1/1A2/1B1 and 2E1	Mikstacka et al. (2007)
	Decreases the action of NF-kB	Mikstacka et al. (2007)
	Downregulates expression of Cyclin D1, p21, p27, p53, Bax/Bcl-2 Inhibits of MEK/ERK, PI3eK/Akt signaling pathways	Limer and Speirs (2004)
	Inhibit expression of Bcl-2, and promote apoptosis	Nguyen et al. (2008)
Pterostilbene	Increase Caspase 3/7, caspase 3, GP_X Bax and P53 activity.Decreases Bcl-2, Akt and MMP Causes prolongation of S-phase; Inhibit the activity of CYP-1A1/1A2/1B1 and 2E1	Suh et al. (2007)
	Decrease the activation of NF-kB	Mikstacka et al. (2007)
Coumestrol	Promotes senescence through the p53–p21 pathway by inducing ROS production	Lee et al. (2013)
Sesamin	Tumor supression via downregulating the expression of EGFR and MAPK	Majdalawieha et al. (2017)
Matairesinol, Secoisolariciresinol	G0/G1 mitotic phase arrest in breast cancer cells causes 60% reduction in cancer cells	Abarzua et al. (2012)

DNMT1 DNA (cytosine-5)-methyltransferase 1; *hTERT* human telomerase reverse transcriptase; *MAPK:MEK* mitogen-activated protein kinase; *PI3K* phosphatidylinositol-3-kinase; *Bcl-2* B-cell lymphoma 2; *Bax* Bcl 2 associated X protein; *ACF* aberrant crypt foci; *MMP* matrix metallopeptidase; *FAK* focal adhesion kinase; *EGFR* epidermal growth factor receptor; *CK-2* casein kinase 2; *PR* progesterone receptor; *CYP* cytochrome p 450; *CDK* cyclin dependent kinase; *Akt* protein kinase B; *NF-KB* nuclear factor kappa B; *IGF* insulin-like growth factor; *p21 WAFI* cyclin-dependent kinase inhibitor

is limited. Newer drug therapies mainly aim to maintain insulin and androgen levels. The treatment includes insulin-lowering agents, oral contraceptives or anti-androgens, and lifestyle modifications. As the treatment for PCOD is limited recently, diet modification has received much scientific attention (Mansour et al. 2016; Rajan et al. 2017). A study by Rajaei and colleagues demonstrated that treatment with genistein shows normal granulosa and theca cell layers and well-developed antral follicles in the ovary. They also exhibited a beneficial role in PCOD by decreasing oxidative stress or estrogen pathways (Rajaei et al. 2019). In women with PCOD, genistein (18 mg/twice a day) intake significantly decreased LH ($p < 0.001$), testosterone ($p < 0.001$), and dehydroepiandrosterone sulphate (DHEAS) ($p < 0.001$). It also reported that phytoestrogens might have an advantage in improving lipid profile in women with PCOD (Khani et al. 2011). Another clinical study reported that soy supplementation significantly decreased insulin levels ($p < 0.001$), HOMA-IR ($p < 0.001$), serum testosterone ($p < 0.01$), and DHEAS compared to the placebo group (Jamilian and Asemi 2016).

It was observed that soy isoflavones could significantly improve testosterone, LH, prolactin, estrogen, insulin levels, and lipid profile in a rat model of PCOD. However, it failed to produce a change in progesterone or FSH level (Manzar et al. 2021). In another study, soy isoflavones demonstrated its beneficial role in rats with PCOD by inhibiting aromatase activity. The observed effect is attributed to the capacity of isoflavones to lower testosterone concentrations in the peripheral circulation (Rajan et al. 2017). The influence of the flaxseed-rich diet on hormonal imbalance, pregnancy rate, and the regular menstrual cycle of 32 women with PCOD was studied in a clinical trial. The study results showed that 33.3% of patients had a regular menstrual cycle, 16.7% reported a change, and 10% became pregnant after receiving a flaxseed-rich diet (Farzana et al. 2015; Najafi et al. 2018). Resveratrol also lowers DHEAS, ER stress, and testosterone levels in PCOD (Takahashi et al. 2017). A double-blind, randomized trial reported that resveratrol intake could produce a significant decrease in DHEAS, total testosterone, FSH, and insulin level in the intervention group of PCOD patients (Brenjian et al. 2020). In another clinical trial with quercetin, a significant decrease in LH, testosterone, insulin, and HOMA-IR was observed (Banaszewska et al. 2016; Rezvan et al. 2016). It has been reported that phytoestrogens also play an essential role in inhibiting the activity of cytochrome p450, an aromatase enzyme and regulating the steriodogenic pathway. They also decreased the number of ovarian cysts and theca layer thickness (Rani et al. 2022). Dietary intervention with genistein may benefit PCOD patients and may be chosen as an alternate remedy (Khani et al. 2011). The role of phytoestrogen in the management of PCOD is summarized in Fig. 5.

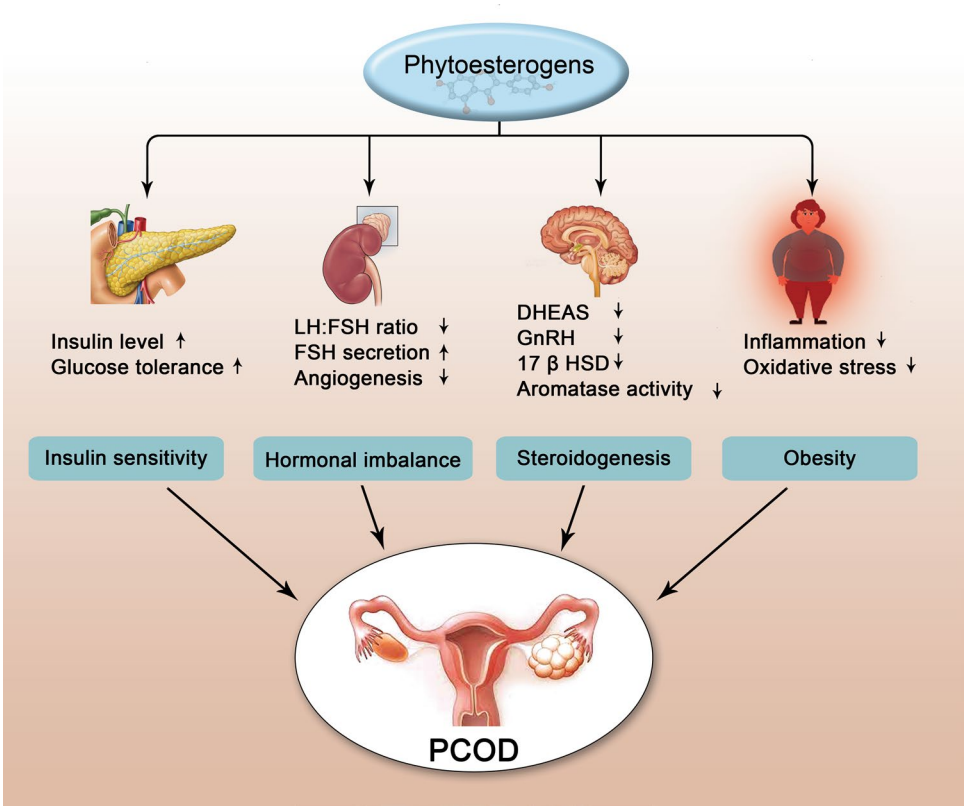

Fig. 5 Effect of phytoestrogen in the management of PCOD. Phytoestrogens increase insulin sensitivity, regulate hormonal imbalance, and steroidogenesis, and decrease obesity

Effect on ovarian cancer

Ovarian cancer is the most common cancer in women, which is characterized by rapid growth, high metastasis, and quick drug resistance. In such cases, therapies that can inhibit disease pathogenesis are needed. Recent studies demonstrate the beneficial effect of phytoestrogen in managing ovarian cancers. In ovarian cancer cell lines, genistein and daidzein (10 and 50 μM) were able to reduce apoptosis by altering FAK and PI3K/AKT/GSK signaling pathways and expression of p21/cyclin D1. These phytoestrogens inhibited cell migration, invasion, and proliferation and induced cell cycle arrest (Chan et al. 2018). Resveratrol inhibits protein glycosylation in cancer cells inducing ER stress-mediated apoptosis in cancer cells that involves Akt/GSK3. Resveratrol also interferes with hexosamine biosynthesis to promote protein glycosylation disruption (Gwak et al. 2016). The meta-analysis showed that phytoestrogen consumption has a preventive effect against ovarian cancer, with increased consumption reducing the risk by approximately 30% (Qu et al. 2014). The mechanistic study in various invitro and in vivo models reveals that they can interfere with the signaling pathways like ER-dependent signal transduction, GnRH-receptor, FSH or LH receptors, and GFR, which helps in regulating hormones and expression of Akt, Raf, caspase3, NF-kB, and Bcl-2. This results in the inhibition of metastasis and cell proliferation and promotes apoptosis in ovarian cancer (Hwang et al. 2013; Lee et al. 2014; Dull et al. 2019).

Effects on postmenopausal symptoms

Menopause is a transition stage in women, characterized by cessation of ovulation because of the decline in estrogen production. The most common vasomotor symptoms in postmenopausal women associated with estrogen deficiency include hot flashes, nocturnal sweats, and sleeplessness. Most women, however, suffer these symptoms during pre-menopause and early post-menopause, resulting in emotional and behavioral issues (such as depression, anxiety, mood swings, inability to focus, and tiredness), causing a substantial impact on one's quality of life. The decreased estrogen levels also may cause an increased risk of cardiovascular disease, osteoporosis, and breast and endometrial cancer. Phytoestrogens also play an ambiguous role in managing postmenopausal symptoms (Carbonel et al. 2018; Thangavel et al. 2019). Extensive work has been reported on the beneficial effect of genistein on post-menopause symptoms. It has a protective effect on osteoporosis, hot flashes, and vaginal dryness and showed benefits in reducing cardiovascular problems, obesity, cancer, and diabetes (Maurida et al. 2018; Júnior et al. 2022).

The effect of regular intake of dietary soy isoflavones was studied in Japanese menopausal women and the results showed that isoflavones significantly reduced the incidence of hot flashes (Nagata et al. 2001). A comparative trial conducted by Crisafulli et al. showed that genistein (54 mg/day) could reduce menopausal hot flashes (Crisafulli et al. 2004).

Preclinical studies show genistein reduces body weight in ovariectomized animals by regulating lipid metabolism. The mechanistic study showed that genistein and daidzein regulate hepatic gluconeogenic and lipogenic enzyme (hepatic fatty acid synthase and carnitine palmitoyltransferase) activities (Choi et al. 2008). After using genistein (54 mg/day) for 1 year, postmenopausal women with metabolic syndrome had a noticeably lower lipid profile, with an increased level of HDL (Squadrito et al. 2013). These results suggest that phytoestrogens, especially genistein, can improve the quality of life in obese subjects with disturbed lipid metabolism caused by natural or surgical post-menopause (Jayagopal et al. 2002; Szkudelska and Nogowski 2007).

Women who are postmenopausal or who have had an ovary surgically removed are more likely to suffer from diabetes mellitus, one of the most frequent lifestyle diseases in the world population. This is mostly because of the absence of ovarian hormones, which regulate glucose metabolism. The beneficial effect of phytoestrogen in glucose homeostasis is believed to be because ofeither estrogenic or non-estrogenic mechanisms. A meta-analysis by Zhang et al. found that isoflavone intake can significantly reduce fasting blood glucose in non-Asian postmenopausal women (Zhang et al. 2013). In a 1-year-long trial using genistein supplements (54 mg/day, n = 60), a significant reduction in HOMA-IR, fasting glucose, and insulin concentration in postmenopausal women with metabolic syndrome was observed. Interestingly, the short-term phytoestrogen supplementation produced no significant antidiabetic effect in clinical studies (Kim et al. 2013).

Studies in rodent models with soya isoflavones have shown reductions in blood glucose levels and improved glucose tolerance/insulin sensitivity (Nakai et al. 2020; Martín and Ramos 2021). In another 6 months clinical trial using soy isoflavones (100 mg/day), a significant reduction of FG (20.5%) and insulin (58.3%) in postmenopausal women was reported (Cheng et al. 2004). In a randomized, placebo-controlled trial of purified soy isoflavone (40 mg/day) in postmenopausal women, it was observed that a significant reduction in FG concentrations compared with the placebo group was observed. However, the study showed that there was no significant effect on lipid concentrations (Ho et al. 2007). The pancreatic islet cells are affected by the protein tyrosine kinase inhibitor genistein, which increases insulin secretion. In obese diabetic mice, dietary genistein consumption decreased hyperglycemia, glucose tolerance, and blood insulin levels via protecting β-cells (Fu et al. 2010).

The loss of functional cell mass caused by apoptosis characterized both type 1 diabetes and type 2, and

islet-cell proliferation plays a critical role in cell adaptation to increased apoptosis and insulin resistance, making it a promising therapeutic approach. These discoveries might cause the creation of brand-new, all-natural diabetes prevention and treatment medications (Bhathena and Velasquez 2002; Fu et al. 2010).

Due to low estrogen, cardiovascular diseases are often observed in postmenopausal women. According to a clinical study, 54 mg of genistein has a cardioprotective effect on population. (De Gregorio et al. 2017). Deodato et al. found that administering intravenous genistein lowers myocardial necrosis, serum CPK, myocardial contractility, and ventricular tachycardia in a clinical study. In postmenopausal women, genistein significantly decreased myocardial ischemia and reperfusion injury, supporting its role as a cardio-protective drug (Amerizadeh et al. 2022).

Phytoestrogens also find application in the management of mental disorders. A reduction in estrogen levels triggers these conditions in postmenopausal women. Based on a preclinical study, Shen and colleagues reported genistein inhibits the expression of the depression gene, microRNA miR221/222, and increases the effect of Cx43, which has anti-depressant action (Shen et al. 2018). According to studies, genistein may also cross the blood–brain barrier and bind to ER-β receptors in the hippocampus more strongly than ER-α. It also functions as an antidepressant by controlling monoamine oxidases (MAO) activity and preventing serotonin release. (Baffa et al. 2010; Gupta et al. 2015; Shen et al. 2018). Animal studies reveal phytoestrogen acts by several mechanisms in anxiety disorder. The key mechanism involves decreasing the level of superoxide dismutase and MAO (Evans et al. 2011; Thangavel et al. 2019).

Estrogen insufficiency, which speeds up bone loss and promotes bone resorption, is the primary factor contributing to postmenopausal osteoporosis. As phytoestrogen has structural similarity with 17-beta-estradiol, they play an important role in maintaining bone mineral density (BMD), bone turnover markers, and the mechanical strength of the bone (Pankova and Tsvetkova 2015). The action of isoflavones is mediated through their binding to estrogen receptors of the target cell and can help in estrogen replacement. Genistein promotes osteoblast function while inhibiting osteoclast activity and appears to be the most beneficial in maintaining bone health (Al-Anazi et al. 2011). A study by Wang et al. demonstrated that genistein 7-*O*-phosphate, a derivative of genistein with high bioavailability, could prevent osteoporosis by controlling the decline in BMD. It showed a better osteoprotective effect than genistein in ovariectomized rats (Wang et al. 2019).

It has been demonstrated that soy isoflavones reduced osteoclast activity in in-vitro studies (Tadaishi et al. 2014). In a systematic review of randomized, controlled trials, it was reported that phytoestrogen can stimulate osteoblast proliferation, prevent bone loss, and help in maintaining reduced bone health during menopause (Abdi et al. 2016). Coumestrol affects osteoblasts and osteoclasts, resulting in higher bone density and less bone resorption (Pankova and Tsvetkova 2015). Bioactive flavonoids help enhance the production of new bone and inhibit bone resorption by modulating the cell signaling pathways that control osteoblast and osteoclast growth (Pankova and Tsvetkova 2015). The in-vitro cell line studies suggest that the 8-prenylnaringenin interferes with bone metabolism through the ERα signaling pathway. 8-Prenylnaringenin enhanced the differentiation and maturation of osteoblast while it inhibited the differentiation of the osteoclast cell line, and interestingly the effect was more substantial than genistein and daidzein (Luo et al. 2014). The osteogenic and anti-resorptive effects of resveratrol have been reported in the different in-vitro mechanistic study suggests that it promotes proliferation and differentiation of osteoblastic in cell lines via non-genomic signaling pathway, ER-dependent ERK1/2 activation (Dai et al. 2007; Mobasheri and Shakibaei 2013). Table 3 summarizes the various clinical trials of phytoestrogen in reproductive health.

Conclusion

Phytoestrogens with a wide range of therapeutic activities have shown benefits in managing diseases such as cancer, PCOD, and various health issues in postmenopausal women. They are beneficial in combating symptoms and conditions caused by estrogen deficiency, which is thought to be the primary reason for their positive effect on pre-menopausal and postmenopausal women. The therapeutic options available for clinicians are limited in several areas of reproductive health, and these phytoestrogens can play a significant role in filling the gap in these areas. The risk of consuming phytoestrogens is unknown and should be a critical part of future research. Based on the currently available evidences presented in this review, we can conclude that the consumption of phytoestrogens have specific physiological effects on human reproductive organs. These effects are mostly connected to hormone regulation, but like hormones, the advantages depend on the stage of life. Only a few studies examined the impact of phytoestrogens during pregnancy and adolescence. Also, the interventions with phytoestrogens in disease conditions such as the uterus and cervical/vaginal cancer are not well established. Despite extensive data from in vitro, preclinical and clinical studies, very few marketed phytopharmaceuticals from this category are available as a therapeutic agent for effectively addressing reproductive health issues, except soya/flaxseed-based health foods/nutraceuticals.

Table 3 Clinical studies of phytoestrogen in reproductive health

Phytoestrogen	Target	Result	References
Isoflavones	Semen quality and serum sex steroid and gonadotrophin levels	No observable effect on semen quality or hormone levels	Barratt (2001)
Genistein	Pituitary gland	Stimulate the rapid release of the hormone and enhanced synthesis of LH	Polkowska et al. (2004)
Genistein	Growth hormone	Stimulate the secretion of growth hormone and affect the level at CNS	Misztal et al. (2007)
Genistein	Sperm motility	Alter the sperm motility along with loss of post-implantation embryo	Eustache et al. (2009)
Isoflavones (soy formula)	Reproductive health in young adulthood, those who are exposed to soy-based formula in infancy	Slightly longer duration of menstrual bleeding	Strom et al. (2001)
Soy food	Breast cancer	Decrease mortality	Alipour et al. (2015)
Isoflavones	PCOD	Reduce PCOD with a decrease in insulin and testosterone level	Swaroop et al. (2015), Jamilian and Asemi (2016)
Daidzein	Uterine function	Activates estrogen receptors by releasing ovarian estradiol	Khaodhiar et al. (2008)
Genistein	Prostate cancer	Reduce expression of prostate cancer biomarker KLK4 and cell cycle gene, chemopreventive effect	Lazarevic et al. (2012)
Daidzein	Hot flashes in menopausal women	Reduces hot flashes	Khaodhiar et al. (2008)
Isoflavones and lignans	Depression among menopausal women	Relieve depression symptoms	Li et al. (2021)
Quercetin	Insulin resistance and hormonal profile of women with PCOD	Increase the level of adiponectin by 5.56% Significantly ($p < 0.001$) reduced HOMA-IR and hormonal profile (testosterone, LH)	Rezvan et al. (2016)

LH leutinizing hormone; *ER* estrogen receptor; *CNS* central nervous system; *KLK4* Kallikrien related peptidase 4

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Declarations

Conflict of interest The authors declare no conflict of interest, financial or otherwise.

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