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Association between Phytoestrogen Consumption and Female Reproductive Health: A Systematic Review of Experimental Models

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Abstract

Phytoestrogens have been shown as promising therapeutic agents for the treatment of menopausal symptoms, osteoporosis, breast cancer, and cardiovascular diseases. However, due to its unique chemical structure, phytoestrogen may cause unintended estrogenic and/or antiestrogenic effects on the human body, especially with regard to female reproductive health and performance. Hence, this systematic review aims to provide a critical evaluation of in vitro and in vivo evidence from the literature regarding the adverse effects of phytoestrogens on female reproductive health. The literature search was performed on four electronic databases including Scopus, Science Direct, PubMed, and Google Scholar following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A total of 965 studies were screened but only 58 of them were found to be relevant and assessed for eligibility. Of these, 23 studies met the eligibility criteria while the remaining studies were excluded due to insufficiently described methods and lack of clear findings being reported. From the review, phytoestrogens may alter the development of reproductive organs, prolong the estrus cycle, induce the accumulation of fluid in the uterus, and inhibit ovulation. The concentration and exposure duration of phytoestrogens may have different effects on the reproductive organs. Thus, further studies are warranted on the toxicodynamic, toxicokinetic, mode of action, and mechanism of actions of phytoestrogens on the female reproductive system to establish recommendations regarding phytoestrogen supplement consumption for women.

Keywords

- estrogen
- female reproductive organs
- phytoestrogen
- reproductive health

Introduction

Phytoestrogens are natural compounds present in a wide range of daily food, such as soy, legumes, fruits, vegetables, and grains. Phytoestrogens can be divided into isoflavones, coumestans, flavanols, and lignans. The structural compound of phytoestrogen is similar to the 17β-estradiol, thus allowing it to interact with estrogen receptors (ERs) and exert estrogen-like actions.[1] Phytoestrogens are widely consumed by people in Asian regions, especially in China, Japan, Indonesia, and Korea.[2] The mean consumption of isoflavones in Asian countries is approximately 15 to 50 mg/day, much

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higher compared with 2 mg/day among the Western population.

In the literature, phytoestrogens have been suggested to alleviate conditions associated with menopausal symptoms such as hot flushes, either through high consumption of phytoestrogen in natural foods or via supplements.[3] Also, the administration of phytoestrogen seems to exert positive impacts on bone formation in postmenopausal women.[4] Besides, they are also cardioprotective owing to their effects in reducing cholesterol levels in the plasma, thus leading to delayed atherosclerosis and improved vascular functions.[5,6]

In view of their abilities to bind to ERs and act as an estrogen agonist and/or antagonist, phytoestrogens are classified as endocrine-disrupting chemicals (EDC). EDC refers to chemicals that can disrupt the development of the brain, as well as the reproductive and immune systems by interrupting the hormonal balance in the body.[7] Disturbance effects of phytoestrogens on reproductive system of farm animals such as sheep and cows have been reported in previous studies whereby animals fed with plants rich in estrogen suffered from infertility.[8] Other adverse effects of phytoestrogens intake on the reproductive health of female humans have also been reported[9] in which young females fed with more soy products during infancy experienced a higher risk of menarche in early adolescence, likely due to mild endocrine-disrupting effects following the exposure to soy isoflavone.

Although other studies have reported the benefits of dietary phytoestrogens in combating menstrual issues and postmenopausal osteoporosis, a critical analysis regarding reproductive disturbances following phytoestrogens consumption is vital to present the relevant evidence to scientists to support the need for further research on phytoestrogen properties and the impact of prolonged exposure. This review systematically identified and evaluated different types of phytoestrogen and their effects on female reproductive health based on both in vitro and in vivo experimental findings.

Methodology

Search Strategy

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[10,11] The article search was executed through Scopus, Science Direct, PubMed, and Google Scholar databases to identify relevant articles published between 2011 and 2020. A wide range of keywords was used, including "phytoestrogen" AND "reproduction" OR "sexual function" OR "fertility" OR "uterus" OR "uterine" OR "ovary" OR "vagina" OR "cervix" OR "fallopian tube."

Inclusion and Exclusion Criteria

The inclusion criteria of this systematic review were full-text articles published in the English language, in vitro studies with phytoestrogen added directly into the cell culture, and in vivo studies with oral or injected phytoestrogen administration. We excluded studies that used phytoestrogen supplements that have been mixed with other extracts, as well as those that involved human subjects or lacked reporting of reproductive outcomes. Review articles, letters, conference abstracts, and editorials were also excluded from this systematic review.

Study Selection

Two independent investigators performed the search to select the relevant articles from the databases. Titles and abstracts were examined to identify relevant studies that met the inclusion criteria. Afterward, full-text reading of the articles was performed to confirm the inclusion criteria. Any disagreements were resolved by a consensus between both investigators.

Data Extraction and Analysis

The information extracted from eligible articles included the type of phytoestrogen, cell lineage used, tested concentration/dose, administration route, and main findings.

Results

Literature Search

The total number of articles retrieved from the databases was 1409. Of those, 444 duplicates were removed. After screening the abstracts, 907 articles deemed irrelevant to the research question were removed. The remaining 58 articles were assessed for eligibility and critically appraised using the listed criteria. After assessing the full-text articles, only 23 articles met the inclusion criteria, while 35 articles were excluded due to insufficient description of the methods and lack of clear findings being reported. ►**Fig. 1** shows the summary of the search strategy.

In Vitro Experimental Studies

Five studies in this systematic review reported the effects of phytoestrogens on female reproductive function in vitro. In these studies, different types of phytoestrogens were investigated, with isoflavones being the most studied phytoestrogens (three studies) (►**Fig. 2A**). This was followed by an equivalent number of studies investigating coumestans or flavanones. Isoflavones that were studied included genistein and daidzein, while coumestrol and naringenin were the studied coumestans and flavanones. The concentration of phytoestrogen used in the cell culture experiment ranged from 0.05 to 50 μM and the exposure duration varied across studies from 18 to 96 hours. Overall, phytoestrogen concentration was shown to negatively impact reproductive function in a dose-dependent manner.

We found that four of the in vitro studies investigated the effects of phytoestrogens on ovarian follicle growth, while the remaining research studied its impacts on oviductal epithelial cell growth (►**Fig. 2B**). The ovarian follicles investigated were from mice, porcine, and cows, while the oviductal epithelial cells were obtained from bovine. The study findings suggested that phytoestrogens may alter the oviductal microenvironment, inhibit bovine oviductal epithelial cell proliferation and migration, inhibit antral follicle growth, inhibit progesterone production and follicle maturation, reduce ovulation frequency, increase secretion oxytocin, as well as promote abnormal

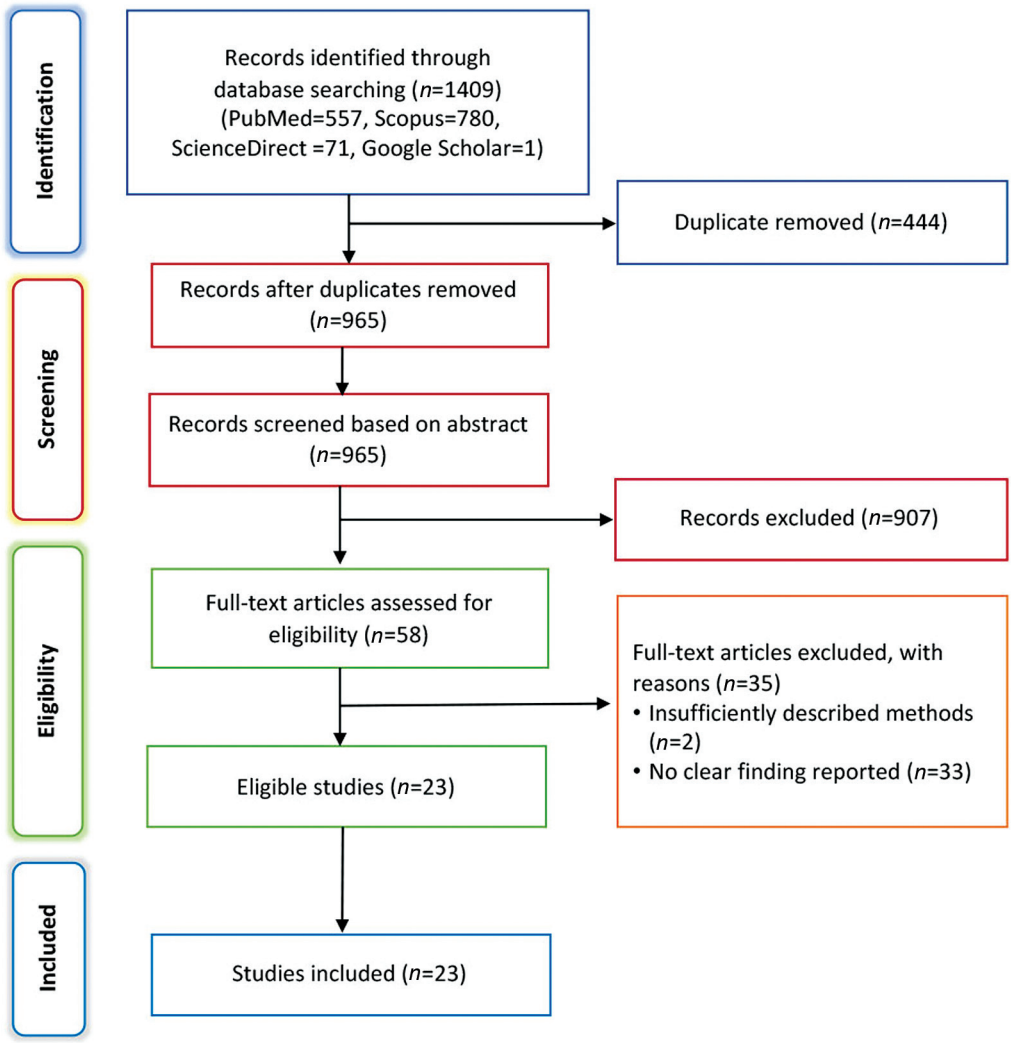

Fig. 1 Flowchart of the study-selection process.

oocyte maturation.[12–16] ►**Table 1** summarizes the description and comparison of the reproductive toxicity of phytoestrogens in vitro.

In Vivo Experimental Studies

Next, eighteen studies in this systematic review reported the effects of phytoestrogens on reproductive health using animal experimental models. Of these, seventeen studies investigated the effects of isoflavones, while the remaining studies investigated flavones (►**Fig. 3A**). Isoflavones used in these studies included genistein, daidzein, biochanin-A, and equol while flavones used was baicalein. Phytoestrogen was introduced either by oral ingestion (solid or liquid form), subcutaneous injection, or intraperitoneal injection. The concentration of phytoestrogen introduced ranged from 0.5 to 291 mg/kg/day, while the exposure duration toward the animal lasted from 3 days to 16 weeks. A short duration of phytoestrogen exposure (3 days) inhibited early folliculogenesis phase,[17] while a longer exposure duration (16 weeks) with a high dose of equol was found to alter the weight and morphology of the uterus and vagina in female mice.[18] Moreover, microbiota status and estrous cycle stage also showed significant alterations after 16 weeks of phytoestrogen exposure, suggesting that a higher concentration of phytoestrogen and longer exposure time negatively affected female reproductive organs.

From the review, a variety of female animal models were applied, such as Wistar mice, Sprague–Dawley rats, apolipoprotein E null (ApoE null) mice, Institute of Cancer Research mice, and CD-1 mice. The ages of the animals ranged from 1 day old to 3 months old. The majority of the in vivo studies in this review investigated the effects of phytoestrogen on the uterus (15 studies), while nine studies focused on the ovaries (►**Fig. 3B**). A few other studies investigated the effects of phytoestrogens on the oviduct and vagina. Genistein, being the most studied phytoestrogen, was found to interrupt reproductive organ development[19–23] besides contributing to an increased fluid accumulation in the uterus.[19,20,24,25] Furthermore, it also prolonged the estrus cycle[26] and inhibited ovulation,[17,20] both of which could lead to infertility. Another isoflavone, that is, daidzein, was shown to modify uterus function at a preimplantation time, promote endometrial squamous metaplasia and abnormal folliculogenesis, as well as lengthen the vaginal estrus

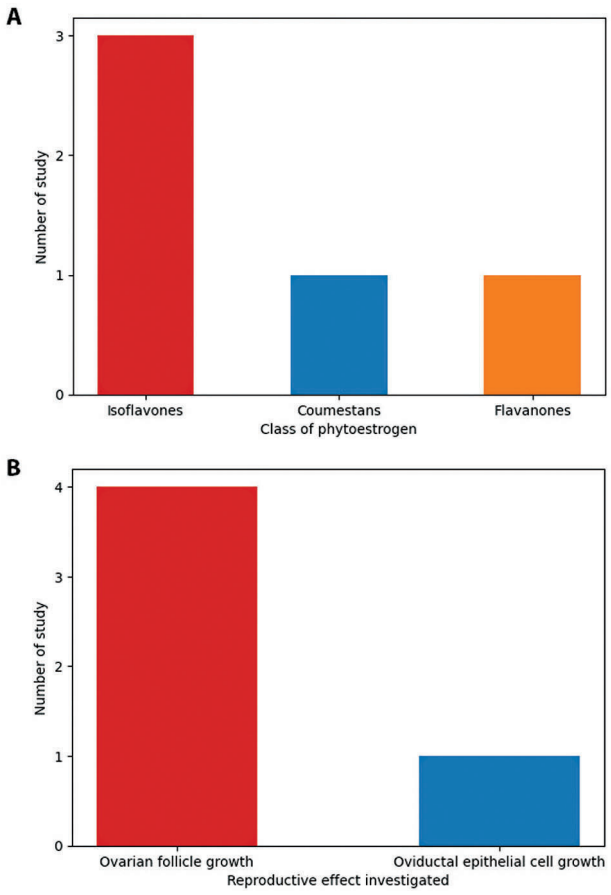

Fig. 2 (**A**) Number of in vitro studies reported on the different type of phytoestrogens. (**B**) Number of in vitro studies investigated phytoestrogen effects on respective reproductive functions.

cycle.[22,23] ►**Table 2** provides a summary of the in vivo studies on the reproductive toxicity of phytoestrogens in female animal models.

Discussion

Effects of Different Types of Phytoestrogen on Reproductive Functions

With regard to the 23 studies included in this systematic review, phytoestrogens that were reported to cause adverse effects on the female reproductive system were those of the isoflavones (daidzein, genistein, biochanin-A, equol), coumestans (coumestrol), flavones (baicalein), and flavanones. Isoflavones were the most studied phytoestrogens, likely attributed to their presence in most of the soybean-based dietary products, including food for humans and other livestocks.[35] Phytoestrogen consumption has been reported to contribute to adverse effects, especially on reproductive functions.[36] However, phytoestrogen of different classes may act similarly to estrogen, causing either weak estrogenic or antiestrogenic effects. The chemical structure of phytoestrogens is characterized by phenolic rings with two hydroxyl groups that are crucial in the ligand anchoring for ER binding. ER can present as subtypes ERα and ERβ, both of which are distributed in the brain, heart, kidneys, lungs, and reproductive organs.

Next, genistein was the most researched phytoestrogen among the studies in this review, possibly because of its abundance in soy-based food products. Owing to its structure, genistein displays a high binding affinity for ERβ. However, the removal of one or two hydroxyl groups will

Table 1 Summary of reproductive toxicity of phytoestrogens performed in vitro

Class of phytoestrogens	Compound	Concentration used (μM)	Exposure duration (hours)	Cell type	Effect investigated	Reference
Isoflavones	Genistein	0.2, 2, and 10	24	Primary cultures of bovine oviductal epithelial cells (BOEC)	Inhibited BOEC proliferation and migration	12
	Genistein	6 and 36	18–96	Antral follicle from female CD-1 mice	Inhibited antral follicle growth	13
	Daidzen	0.05, 0.5, 5, and 50	48	Granulosa cells isolated from porcine ovaries	Inhibited progesterone production of granulosa cells and increased estrogen receptorβ (ERβ) protein expression	14
Coumestans	Coumestrol	1	48	Luteal cells of 3–5, 6–8, and 9–12 weeks of pregnancy from cows	Decreased prostaglandin E2 (PGE2) secretion by luteal cells	15
Flavanones	Naringenin	0.1, 0.3, 1, and 3	42	Cumulus-oocyte complexes (COCs) from pre-pubertal gilts	Impaired cumulus expansion and oocyte maturation	16

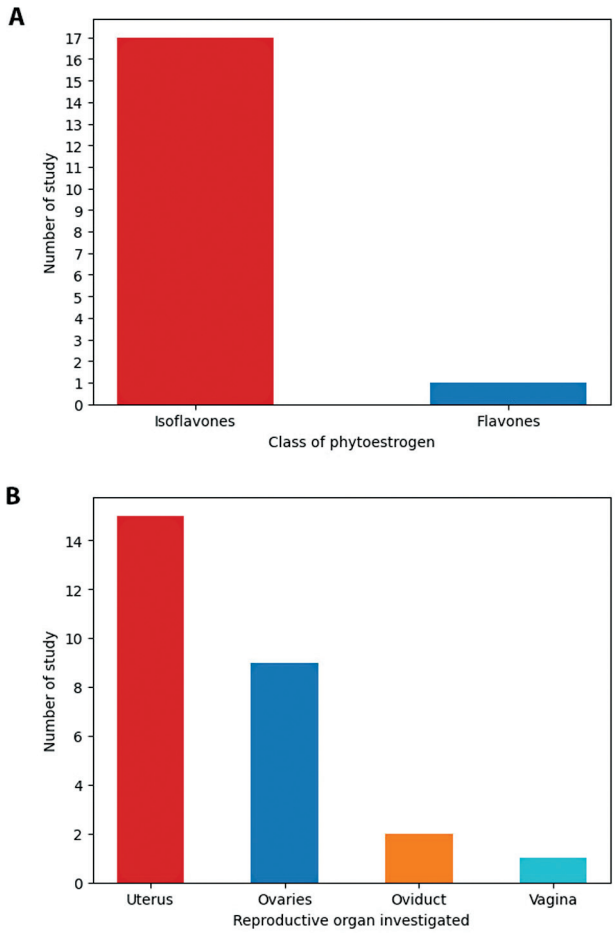

Fig. 3 (A) Number of in vivo studies reported on the different type of phytoestrogens. (B) Number of in vivo studies investigated phytoestrogen effects on respective reproductive organs.

lead to a large loss of binding affinity.[37] Genistein has been shown to affect hypothalamic pituitary gonadal axis by exerting estrogenic and/or antiestrogenic effects.[38] Carbonel et al reported that when animals were fed with a high concentration of daidzein (250 mg/kg/day), the levels of estrogen and progesterone dropped initially,[23] consistent with another study that linked soy-based diet consumption with a decrease of 20 to 33% of the estradiol and progesterone levels in women.[39] In terms of its structure, daidzein can bind to both ERα and ERβ because it exhibits a similar structure to that of estradiol. However, daidzein has a more effective binding to ERβ[40] and its expression can be enhanced above the maximum levels compared with estradiol.[41]

Effect of Dose and Time Exposure of Phytoestrogen

Based on the study by Wu et al, the size of the uterine cavity and wall enlarged when the uterus was exposed to 100 mg/kg of phytoestrogen for ten days[20] due to the oversecretion and accumulation of mediated luminal fluid in the uterus cavity after being triggered by the high amount of phytoestrogen. Similar findings were reported by Chinigarzadeh et al in which genistein shows dose-dependent effects of luminal fluid secretion when ovariectomy rats were exposed to a high dose (50 and 100 mg/kg/day).[25] Following the suspension of phytoestrogen consumption for 2 weeks, the size and volume of the uterus gradually decreased and returned to normal. This suggests that the estrogenic response in the uterus has reduced following the absence of phytoestrogen, hence emphasizing the varying impact of phytoestrogen concentration (dose administered) on the reproductive organs. Nevertheless, the possibility of molecular-level phytoestrogen effects cannot be ruled out despite the uterus regaining its normal size.

In other phases, phytoestrogen acts as an estrogen agonist that stimulates the transition of folliculogenesis from preantral to antral, thus altering the ratio of the follicular and ovarian stroma. Therefore, the pharmacokinetics of phytoestrogen may influence its effect on reproductive organs via different physiological pathways. The exposure duration and dosage also play a role in influencing the kinetics of phytoestrogen in terms of absorption at the target site, distribution to the site of action, and excretion of phytoestrogen from the body.[28,29]

Adverse Effects of Phytoestrogen on Reproductive Performance

Even though phytoestrogens have weaker physiological effects than estradiol, they can still function as endocrine disrupters and induce developmental and reproductive disorders.[42] The endocrine system controls the balance in the growth and development of the reproductive process to ensure a state of homeostasis. Any interruption in the endocrine system may contribute to long-lasting effects on reproductive development and function.[43] It has been shown that ewes fed with clover-rich food eventually produced offspring with abnormal reproductive organs, apart from experiencing infertility problems and a higher chance of miscarriage.[44]

In this systematic review, the in vivo studies highlighted that the adverse effects of phytoestrogen on female reproductive performance mainly occur in the ovaries, oviduct, uterus, and vagina. In the ovaries, these adverse effects could lead to altered structural development of ovaries,[21] disturbance of ovarian follicle development,[17,29] increased follicular atresia,[18] and premature depletion of oocytes.[22] Based on the human studies by Jefferson, high consumption level of soy products in women's diets might compromise ovarian performances, particularly causing hormone imbalance.[45] Since the primary function of the ovary is to produce estrogen, especially in the ovulation stage, high levels of phytoestrogens (>50 mg/kg/day isoflavones) may restrain the production of endogenous estrogen, subsequently inhibiting follicular development.[17,18,20] Altered follicle growth has been shown to delay the time to luteinizing hormone surge, thus requiring more time for estradiol production. In addition, impaired ovarian epithelial function in the presence of antiproliferative activity also causes abnormal folliculogenesis, cystic follicles, and long estrus cycle.[18,26,28,34]

Infertility is commonly caused by implantation failure secondary to the uterine environment or hormonal milieu that is not conducive for implantation to occur. If

Table 2 Summary of reproductive toxicity of phytoestrogens performed in vivo

Class of phytoestrogens	Compound	Exposure route	Dose of phytoestrogen	Exposure duration	Animal used	Animal age	Reproductive organ studied	Reference
	Genistein	Subcutaneous injection	50 mg/kg/day	3 days	Female Wistar rats	17 days old	Ovaries	[17]
Isoflavones	Equol	Oral	291 mg/kg	16 weeks	Female ApoE null mice	6 weeks old	Ovaries, oviduct, uterus and vagina	[18]
	Genistein	Subcutaneous injection	25, 50, and 100 mg/kg/day	6 days	Female Sprague–Dawley rats	3 months old	Uterus	[19]
	Genistein	Subcutaneous injection	100 mg/kg/day	10 days	Female ICR mice	Pup (day 1)	Ovaries and uterus	[20]
	Daidzein and genistein	Subcutaneous injection	2 mg daidzein/kg/day + 5 mg genistein /kg/day	5 and 10 days	Female CD-1 mice	Pup (day 1)	Ovaries and uterus	[21]
	Soy isoflavones (genistein, daidzein and glycerin)	Oral	50, 100, or 200 mg/kg	3 months	Female Wistar rats	21 days old	Ovaries and uterus	[22]
	Daidzein and genistein	Oral	42, 125, and 250 µg/g/day	30 days	Female Wistar EPM-1 rats	90 days old	Uterus	[23]
	Genistein	Subcutaneous injection	25, 50, and 100 mg/kg/day	7 days	Female Sprague–Dawley rats	3 months old	Uterus	[24]
	Genistein	Subcutaneous injection	25, 50, and 100 mg/kg/day	3 days	Female Sprague–Dawley rats	3 months old	Uterus	[25]
	Genistein	Oral	25 mg/kg/day	Uterus exposure to postnatal day 80	Female ICR mice	Pup (day 1)	Ovaries and uterus	[26]
	Genistein	Subcutaneous injection	50 mg/kg/day	5 days	Female CD-1 mice	Pup (day 1)	Uterus	[27]
	Genistein	Subcutaneous injection	25, 50, and 100 mg/kg/day	7 days	Female Sprague–Dawley rats	Adult (not specified)	Uterus	[28]
	Genistein	Oral	10 and 100 mg/kg/day	3 weeks (postnatal day 22–42)	Female Sprague–Dawley rats	Postnatal day 22	Ovaries and uterus	[29]
	Genistein	Subcutaneous injection	0.5, 5, 10, 25, 50, and 100 mg/kg/day	3 days	Female Sprague–Dawley rats	3 months old	Uterus	[30]
	Genistein	Subcutaneous injection	50 mg/kg/day	5 days	Female CD-1 mice	Pup (day 1)	Oviduct	[31]
	Biochanin-A	Intraperitoneal injection	25, 50, and 100 mg/kg	4 days (12^{th},14^{th},16^{th} and 18^{th} utero exposure)	Female rats	Not specified	Uterus	[32]
	Daidzein	Subcutaneous injection	5 and 60 mg/kg/day	Gestation days 6 to 21 during prenatal development	Female Sprague–Dawley rats	Not specified	Ovaries	[33]
Flavones	Baicalein	Oral	30, 60, and 90 mg/kg	Gestation days 11, 13, 15 and 17	Female Wistar mice	35–40 days old	Ovaries and uterus	[34]

Abbreviations: EPM-1,—; ICR, Institute of Cancer Research.

serum hormones reveal no deficits of progesterone and estradiol during early pregnancy in mice, it indicates that hormonal levels are unlikely the causative factors of failed implantation.[46] In contrast, oocytes of poor quality could be a factor that contributes to implantation issues and early pregnancy loss. Further research reported that certain oviductal and uterine conditions were not conducive to maintaining pregnancy. During the transit through the oviduct of phytoestrogen-treated mice, 50% of embryos died. Further embryo transfer trials revealed that the uterus of phytoestrogen-treated mice was incapable of sustaining a pregnancy, even when the blastocysts implanted originated from control animals. These findings suggest that the functions of female reproductive tracts could have been permanently altered, thus explaining the subsequent infertility.

Besides, phytoestrogen may disturb fetal or neonatal development by causing apoptosis to occur following insufficiency in intra-ovarian factors from estradiol.[47] The prolonged effects may include abnormal sexual differentiation, reduced anogenital distance, delayed puberty, disturbed fertility, and lower birth weight. According to Dinsdale and Ward, phytoestrogen exerts adverse effects in obese individuals by affecting their reproductive system, especially exposure that happened during phases of fetal and neonatal development.[48] However, when phytoestrogen was exposed in immature rats, it reduced the concentration of serum insulin and leptin.[49] Therefore, the hypothalamic and ovarian axes remain underdeveloped in young rats, thus affecting the functions of various body mechanisms. Even though the endogenous estrogen level is considered low in immature rats, the administration of phytoestrogen is expected to manipulate the entire cycle and overall level of endogenous estrogen.

Mode of Actions of Phytoestrogens

In this systematic review, only a few studies explained the mode of actions of phytoestrogen that underlined the reproductive performance.[13,17,20,22,25,26] Phytoestrogen may imitate endogenous estrogen action by binding to the ER. The binding affinity of phytoestrogen for ERα and ERβ is weaker compared with that of endogenous estrogen. Therefore, it can exert an agonist or antagonist effect in the presence of estrogen.[26] Phytoestrogens may alter the endogenous estrogen level via interaction with enzymes such as p450 aromatase, 17-hydroxysteroid dehydrogenase, 3β-Hydroxysteroid dehydrogenase, topoisomerases, and tyrosine kinases, in addition to interacting with ERs.[13,20,50] However, compared with endogenous estrogen, phytoestrogen is more stable and does not metabolize rapidly.[51] Among phytoestrogens, isoflavones have the greatest affinity to ERβ than Erα.[52] Even a low concentration of environmental phytoestrogen may lead to an altered biological system response.

In addition, phytoestrogens may potentially impact sex hormone bioavailability by increasing the production of sex hormone binding globulin (SHBG). Some phytoestrogenic substances such as isoflavonoids and lignans inhibit steroidogenic enzymes that promote the reduction of 5α-reductase activity. Consequently, a lower level of testosterone is converted into its active form of dihydrotestosterone. Phytoestrogen may also stimulate or inhibit ERα and/or ERβ protein expression in the neurological and reproductive systems.[53] The production of proteins binding sex hormones that induce SHBG production occurs specifically in the liver. Contrary to estradiol, phytoestrogens have a low binding affinity to SHBG. Hence, they exert an antiestrogenic impact by lowering the level of free endogenous hormones. Moreover, phytoestrogen can prevent thyroxine production and absorption of synthetic thyroid hormone by acting as an alternate substrate to prevent thyroid peroxidase-catalyzed tyrosine iodination.[54] Low thyroid hormone levels can lead to an imbalance of female hormones that disrupts regular ovulation, consequently resulting in infertility and abnormal reproductive function.

Last but not least, other biological effects of phytoestrogen are not uncommon. As an endocrine-disrupting compound, it can affect numerous hormonal systems via various routes. First, phytoestrogen may suppress tumorigenesis via inhibition of protein tyrosine kinases, DNA topoisomerases I and II, as well as other chemoprotective mechanisms.[55] Activation of nongenomic pathways typically results in this interference. The signaling pathway of phytoestrogens involved in mediating toxic effects are phosphatidylinositol-3 kinase (Akt), mitogen-activated protein kinase (MAPK), and nuclear factor-kappa β (NF-Kβ).[56] The functional relevance of this route or its interruption remains unclear. G-protein-coupled ERs, together with ERα and ERβ, play a fundamental role in fast vascular estrogen signaling.[57] Apart from these direct actions for signaling patterns, phytoestrogens may affect epigenetic marks by altering histone methyltransferase activities, DNA methylation, and chromatin remodeling.[58,59]

Conclusion

The findings from both in vitro and in vivo studies included in this systematic review reveal that phytoestrogens may exert adverse effects on female reproductive health such as altered reproductive organ development, prolonged estrus cycle, accumulation of fluid in the uterus, inhibition of ovulation, and increased risk of infertility. Phytoestrogen dosage associated with such effects ranges from 0.5 to 291 mg/kg/day. Moreover, the types of phytoestrogens that contribute to adverse reproductive health effects belong to the subgroups of isoflavones, coumestans, flavanones, and flavones. The impact of phytoestrogens exposure on the uterus, ovary, oviduct, and vagina is determined by dose and time-dependent relationship. Phytoestrogen may also alter the endogenous estrogen level via interaction with enzymes, such as inhibiting steroidogenic enzymes, stimulating inhibiting ERα and ERβ protein expression, acting as an alternate substrate to prevent thyroid peroxidase, as well as modifying the chromatin structure. The signaling pathway of phytoestrogens involved in mediating its toxic effects are Akt, MAPK, and NF-Kβ.

Authors' Contributions

All authors contributed to collecting the data, writing the article, reviewing, and approving the final article.

Compliance with Ethical Principles

The authors confirm that this review has been prepared in accordance with COPE guidelines and regulations. Given the nature of this article, ethical approval is not required.

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Conflict of Interest

None declared.

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