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Adverse effects of phytoestrogens on mammalian reproductive health

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Abstract

Phytoestrogens are nonsteroidal plant-derived compounds found in various forms in humans and animal foods. Phytoestrogens bind with mammalian estrogen receptors (ER) as they are structurally like mammalian estrogen and alter multiple mechanisms and processes, causing several disorders and diseases. Studies in humans and animals have revealed that dietary phytoestrogens play a crucial role in preventing hormone-dependent diseases and disorders such as menopausal symptoms, osteoporosis, cancer, and heart disease. Despite the potential health benefits, phytoestrogens also have several adverse effects on the reproductive health of males and females. Phytoestrogens bind with ER, interfere with the hormonal regulation of the reproductive organs, and increase the propensity of infertility, abnormal estrus cycle, and anestrous. Phytoestrogens also alter prenatal and postnatal fetal development causing various developmental abnormalities. Several studies investigated the effects of phytoestrogen compounds on reproductive health using animals, humans, and in vitro culture models. Therefore, it is important to summarize these findings for future mitigation strategies against phytoestrogens. This review focuses on the impact of specific phytoestrogens on the reproductive health of males and females and the underlying mechanisms involved in the detrimental effects of various phytoestrogen compounds. Based on the evidence obtained from the literature, we also summarized the findings in the tabular form on different reproductive tissues in males and females, including prenatal and postnatal fetal development.

Keywords: Phytoestrogens, Genistein, Endogenous hormones, Reproduction

Phytoestrogen

Phytoestrogens are a diverse class of nonsteroidal, diphenolic, estrogenic plant compounds, including prenylated flavonoids, isoflavones, coumestans, and lignans [1,2]. They are plant-derived nonsteroidal compounds structurally or functionally similar to mammalian estrogen (E_2), especially 17β-estradiol [3,4]. Phytoestrogens have an affinity for estrogen receptor -α (ER α) and -β (ER β) [3,5,6], peroxisome proliferator-activated receptor (PPAR) family [7-9] and the aryl hydrocarbon receptor (AhR) [9–11]. Phytoestrogens or their active metabolites are known to act mainly on male and female central nervous systems and reproductive systems. Phytoestrogens are polyphenolic compounds that include over 100 molecules [12]. According to their chemical structure, they are divided into isoflavones, flavones, coumestans, stilbenes, and lignans (**Figure 1**) [13]. Several plants consumed by humans and animals contain phytoestrogens [14]. Soybean products are rich in higher concentrations of isoflavones, while flaxseed is rich in lignans, clover contains coumestans [15], olives contain flavones [16], and stilbenes are found in cocoa and grape containing products, particularly red wine [15]. Mostly isoflavones from legumes, beans, and bean-containing products exhibit estrogenic activity in animals [17-21]. Second-generation soy foods are made by adding soy ingredients to a wide variety of manufactured foods. These second-generation soy foods such as tofu yogurt and soy noodle contain less isoflavone content [22-24]. Cereals, fruit, and vegetables such as flaxseed (known as linseed) contain a high concentration of lignans [19,25,26], while in whole grain cereals, vegetables, fruit, and seeds have a lesser concentration of lignans [17]. After consumption, phytoestrogens are metabolized by intestinal microflora, conjugated in the liver, distributed to various tissues through plasma, and excreted through urine [27].

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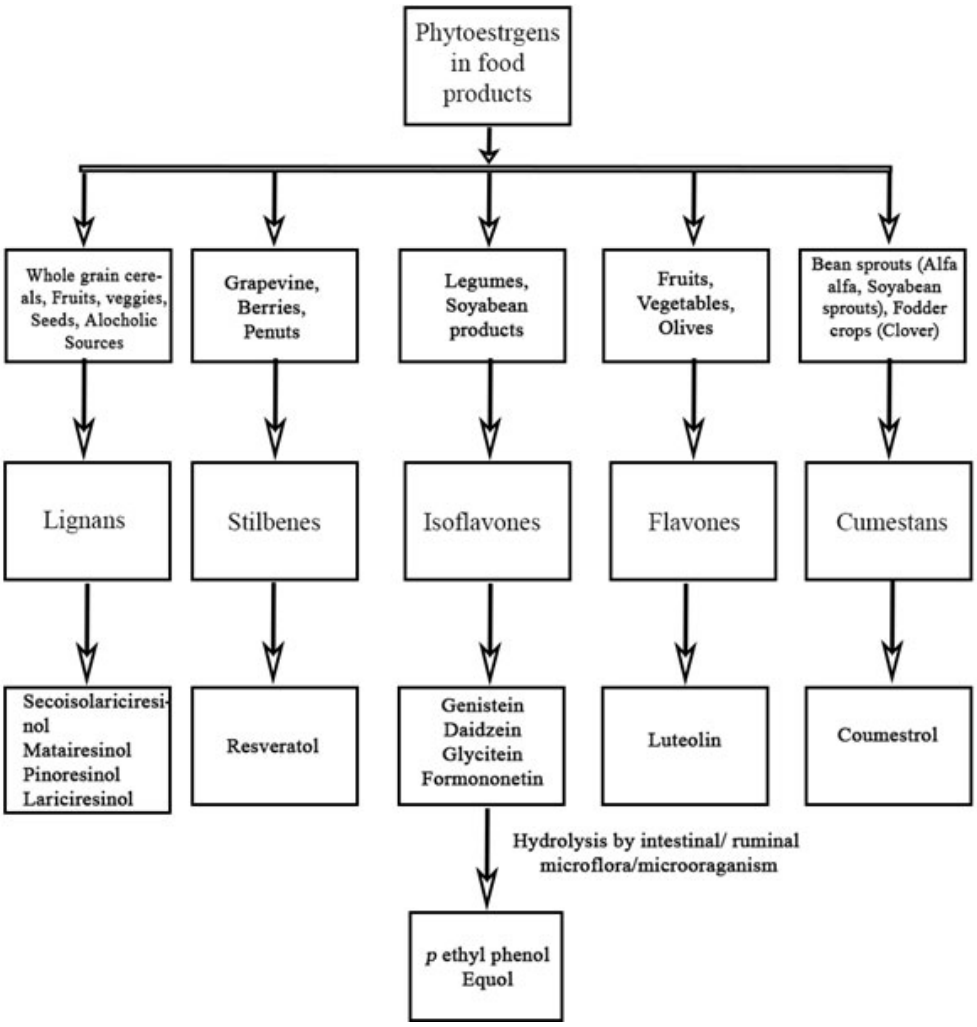

Figure 1. Classification and metabolism of phytoestrogens [15,16,43,44].

The detrimental effects of phytoestrogens depend on the type of compound, dosages and duration of exposure, and the animal species. Although numerous studies have reported the potential health benefit of consuming phytoestrogen compounds, there are several concerns about their negative impact on male and female reproductive health and their consequences on the health and performance of the offspring. Several studies have reported the health benefits of phytoestrogens on the different body systems using individual animal species. However, very few reports examined reproductive health effects in detail, requiring a more comprehensive review utilizing the recent findings from various animal species, including humans. Therefore, this review emphasized the detrimental impact of specific phytoestrogen compounds on male and female reproductive organs and their potential impact on offspring health and performances. This review systematically discussed the findings on phytoestrogen effects on different reproductive tissues in males and females, including prenatal and postnatal fetal development, to formulate mitigation strategies.

Mechanism of Phytoestrogen Action

Phytoestrogens exert their biological effects through classical, genomic, or nongenomic pathways. As they are structurally similar to endogenous E_2, they can potentially bind to nuclear E_2 receptors [**28**]. Like estradiol, phytoestrogens have low molecular weight, contain a phenolic ring for binding with the estrogen receptor, optimal hydroxylation pattern, and a similar distance between two hydroxyl groups in the nucleus as estrogen. These similarities allow phytoestrogens to mimic the estrogen and bind to the estrogen receptor [**29**], resulting in estrogenic or antiestrogenic responses [**4,30**]. Following binding with the estrogen receptor, they relocate to nuclear cytoplasm and bind with DNA or small RNAs transcription control sites ensuing specific gene expressions [**31**]. Compared to endogenous E_2, they have lower affinities for

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ERα and ERβ. So, they exhibit agonist or antagonist activity depending on the presence of E_2 [28]. Several isoflavones act as selective estrogen receptor modulators with a higher affinity to ERβ than ERα [32,33]. Lower concentrations of environmental estrogens can alter the response to body systems as these compounds have a much lower affinity for nuclear receptors than endogenous E_2 [15]. The effects of isoflavones are mediated by several nongenomic pathways, such as oxidative stress, tyrosine kinases, nuclear factor kappa B, and extracellular-signal-regulated kinases [34,35]. The action of isoflavones in the human or animal body is very complicated as they are usually present in vivo as mixtures of numerous dietary components, which can affect various signaling pathways or affect the same pathways in opposing directions [15]. Isoflavones have lower transcriptional activity than estrogen, and to induce this activity, they need 104 times higher concentrations than endogenous estrogen. This higher concentration requirement is achieved due to their higher bioavailability [29]. Isoflavones also serve as ligands for peroxisome-proliferator-activated receptors, the non-classical estrogen receptor GPER1, the estrogen-related receptors, and the aryl hydrocarbon receptor [32,36-38]. Isoflavones have been shown to indirectly alter epigenetic markers, such as the DNA and histone methyltransferases activities, NAD-dependent histone deacetylases, and other chromatin structure modifiers [39-41]. Isoflavone also acted through the competitive inhibition of endogenous E_2 production by aromatase [41,42]. Phytoestrogens can bind or inactivate enzymes such as P_{450} aromatase, 5α-reductase, and tyrosine kinases altering endogenous estrogens concentration. By attaching or increasing the sex hormone-binding globulin's (SHBG) production, phytoestrogens can also influence the bioavailability of sex hormones [29].

Adverse effects of phytoestrogens on mammalian reproduction

Male reproduction

Male fertility is highly impacted when exposed to environmental toxicants and endocrine disruptors at any stage of life. Across the mammalian species, the production of fertile sperm and testosterone is essential for the propagation of healthy offspring [45]. Studies have suggested that phytoestrogens are known to alter male reproductive events, including hormonal concentration (estradiol, testosterone), spermatogenesis, sperm capacitation, and fertility [46]. The effects of phytoestrogens on male reproductive organs are species and compound-specific. Ingestion of fodder containing high coumestrol caused glandular metaplasia in the bovine prostate and bulbourethral glands [47]. Male goat kids on red clover isoflavones diet showed pubertal Leydig cell steroidogenesis followed by significantly higher plasma [48]. Male co-twin marmoset monkeys (seven pairs) fed soy milk formula resulted in standard body weights, penis length, and fertility. However, these monkeys had significantly higher testis weights with the increased number of Sertoli and Leydig cells per testis [49]. In a 52-week study, chronic and sub-chronic oral genistein administration in male beagle dogs resulted in atrophy of the testes and prostate gland and absence of spermatozoa in the epididymis [50].

Adult male mice fed with a soy-rich diet from conception to adulthood showed a 25% reduction in epididymal sperm counts and a 21% reduction in litter size despite exhibiting normal male behavior [51]. Long-term administration of daidzein to male rats caused a decrease in plasma levels of testosterone as well as erectile dysfunction [52]. Similar results of low testosterone levels were observed in adult male rats exposed to a high dose of coumestrol [53]. This decrease in serum testosterone is due to decreased steroidogenesis in testicular Leydig cells caused by isoflavones [54].

In male rats, a diet high in phytoestrogen blocked spermatogenesis, induced germ cell apoptosis [55], decreased the expression of ERα and AR in the cauda epididymis, and increased lipoperoxidation in epididymal sperm [56]. Chronic dietary exposure to genistein combined with vinclozolin (a fungicide considered an endocrine disruptor) reduced sperm count and motility [57]. Mouse and human spermatozoa exposed to genistein and daidzein in in-vitro studies showed that different doses, alone or in combination, accelerate capacitation [58] and acrosome loss, impairing fertility [59]. Exposure to phytoestrogens at an early age disrupts reproductive function in adulthood. The expression of ERα and androgen receptor (AR) in testes in adulthood was reduced in male mice exposed to neonatal genistein treatment without affecting sperm count and motility [60]. Juvenile rats exposed to high-dose daidzein (100 milligrams(mg)/kilograms(kg)) showed impaired penile erection in adulthood [61]. Phytoestrogen diets given in the perinatal period can also decrease steroidogenesis and androgen secretion by testicular Leydig cells in the adult rat [54]. Different classes of phytoestrogens affect mammalian male reproductive functions on different levels leading to various reproductive abnormalities altering the reproductive physiology of males (**Table 1**).

Female reproduction

Studies in humans and animals have revealed that dietary phytoestrogens play a crucial role in preventing hormone-dependent diseases and disorders such as menopausal symptoms, osteoporosis, cancer, and heart disease. Despite the potential health benefits, it is well documented that the consumption of phytoestrogens impairs female reproductive functions, affecting female fertility and offspring health. The detrimental effects of phytoestrogen on the female reproductive tissues vary according to the compounds, duration of exposure, and physiological status of females [27]. The use of legume pasture has been increased exponentially in animal rearing throughout the world. Because some of these legumes contain phytoestrogens such as isoflavones [62], various reproductive abnormalities have been seen in the

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Table 1. Effects of Phytoestrogens on Male Functions.

Animal	Phytoestrogen Compounds	Effects of Phytoestrogens	Refs
In general	Phytoestrogens	• Alter reproductive hormones, spermatogenesis, sperm capacitation, and fertility	[46]
Bovine	Coumestrol	• Glandular metaplasia in the prostate and bulbourethral glands	[47]
Goat	Red clover isoflavones	• Pubertal Leydig cell steroidogenesis • Significant increase in plasma testosterone concentrations during puberty	[48]
Monkey	Soy milk	• Increased testis weights with Sertoli and Leydig cell numbers per testis	[49]
Beagle dogs	Genistein (orally)	• Atrophy of the testes and prostate gland • Absent spermatozoa in the epididymis	[50]
Mice	Soy-rich diet, Genistein	• 25% reduction in epididymal sperm counts • 21% reduction in litter size • Reduce the expression of ERα and androgen receptor	[51,60]
Rats	Isoflavones, Daidzein, coumestrol	• Decreased plasma levels of testosterone and erectile dysfunction • Decreased steroidogenesis in testicular Leydig cells • Block spermatogenesis, Induce germ cell apoptosis • Reduced sperm count and motility, litter size, and increased post-implantation loss	[47,48,49,50,51,52]
Juvenile rats	Daidzein	• Impaired penile erection in adulthood	[61]
Human	Genistein, Daidzein	• In-vitro studies showed accelerated capacitation and acrosome loss, impaired fertility	[58,59]

past. The first reported case of the phytoestrogens effect was in Australia in 1946, known as "clover disease," identified from abnormally high infertility rates, abortion, and reproductive abnormalities in ewes grazing on clover rich pasture [63]. The red clover silage containing isoflavones and alfalfa containing coumestans are associated with infertility in cattle. Cows on these fodders suffered from cystic ovaries, with behavioral abnormalities including irregular estrous, nymphomania, and anestrous [64]. Another study reported an estrogenic syndrome characterized by repeated estrous, abortions, endometriosis, cystic ovaries, false estrous, swollen vulvae, and uterine enlargement shown by cows feeding alfalfa [65] contains coumestans indicating the effects of phytoestrogens present in the plant. Ovariectomized heifers fed 20 kg of 100% red clover silage displayed edema and mucous discharge from the vulva, fluid accumulation in the uterus, elongated teats, and the presence of milky fluid in the mammary glands [66]. Sugar beet silage contains several estrogenic compounds, which, when fed at relatively high levels to cows, result in decreased fertility, ovulation failure, and cystic ovaries [67]. Soybean products (contain high levels of isoflavones) consumption can result in various reproductive abnormalities, including impaired sexual development of animals, irregular estrous cycle, and impaired pituitary and hypothalamus functions [31]. Cows exposed to a chronic soy diet had lower progesterone levels, failed to ovulate, and had higher infertility rates [68,69]. It was also reported that phytoestrogens induced abortions during the first trimester due to low progesterone (P_4) [70].

Several reproductive alterations were also found in sheep exposed to various phytoestrogens. Ewes grazed on subterranean clover exhibited different reproductive abnormalities, including infertility, low lambing rates, prolapsed uteri, dystocia, severe metritis, uterine inertia, temporary labor, fetal death, and cystic endometrium [63]. There were also reduced ovulation, conception rates, permanent infertility [71], along with ovarian and endometrial cysts observed in ewes [72]. Sheep exposed to chronic estrogenic pasture had permanent infertility because the cervix became defeminized and could not store spermatozoa. In ewe, genes responsible for sexual differentiation are not fully deactivated at birth; however, chronic phytoestrogen exposure leads to loss of sexual characteristics in the adult ewe [73].

The effects of phytoestrogens varied markedly according to species. The captive cheetah diet containing a higher concentration of daidzein and genistein from soybeans decreased fertility and veno-occlusive liver disease [74]. In beagle dogs, sub-chronic and chronic exposure to oral genistein increased uterine weights and small decreases in ovarian weights, respectively [50].

Several studies were conducted to clarify the effects and mechanisms by which phytoestrogens modify reproductive functions in animals. Most studies have evaluated genistein and daidzein's effects: the isoflavones consumed by humans in soybeans and soy products. The effects of phytoestrogen

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on the female genital tract depend on the age and duration of exposure. A high dosage (50 mg/kg) of genistein-treated mice showed pregnancy failure as they could not support the pregnancy [75]. Neonatal exposure to phytoestrogen alters the reproductive physiology of females [76]. Perinatal genistein (10 mg/kg or rats 0, 5, 100, 500 ppm) exposure in females resulted in accelerated vaginal opening and altered estrous cycles, advanced pubertal onset, increased the length of the estrous cycle [77], accelerated the onset of persistent estrus, causes abnormal estrous cycles, decreases fertility, delays parturition [75] and decreases the number of live pups in adulthood [78]. Antral follicles from mice cultured with genistein had altered expression of steroidogenic enzymes (*Star, Cyp11a1, Hsd3b1, Cyp17a1*) and cell cycle regulators (*Cdkn1a, Ccnb1, Ccne1*) along with inhibiting follicular growth [79]. Phytoestrogens affect the development of the female mice's reproductive tract. Genistein exposure to neonatal mice had disrupted oviductal morphogenesis in the 'posteriorized' oviduct [80], and also interfered with ovarian differentiation resulting in ovarian malformations indicating impaired fertility due to multi-oocyte follicles and attenuated oocyte cell death [75,81]. Neonatally, genistein-exposed rats had various ovarian defects, including the absence of corpora lutea, the existence of large antral-like follicles with degenerating or no oocytes, and numerous ovarian cysts [83]. Neonatally, genistein-exposed mice had a 35% incidence of uterine tumors by 18 months of age [82]. Perinatal exposure to phytoestrogens such as resveratrol, zearalenone, and Bisphenol-A resulted in a lack of corpora lutea and an extended estrous cycle with accelerated puberty onset in adult female mice [84].

Rats treated with chronic coumestrol in the diet showed early vaginal opening [85]. Immature rats treated with resveratrol for one week had increased uterine weight and glandular morphogenesis [86]. Neonatal coumestrol-exposed mice exhibited reproductive tract abnormalities, vaginal cysts, persistent vaginal cornification, endometrial squamous metaplasia, absence of corpora lutea, increased ceroid deposition in the ovaries, and the presence of hemorrhagic follicles and had abnormal collagen deposition in the uterine wall by 22 months of age [87].

Phytoestrogens also impaired the hypothalamo-pituitary-ovary (HPO) axis. Phytoestrogens inhibited the hypothalamic GnRH pulse generator activity and serum LH levels in rats by mimicking E_2 negative feedback [88,89]. The release of gonadotropins (LH and FSH) were inhibited by phytoestrogens via ER [89,90]. Genistein inhibited oocyte nest breakdown in the ovary and attenuated cell death during mouse oocyte development [75]. Moreover, P_4 and E_2 concentrations in plasma decreased due to genistein [91]. These studies suggested that phytoestrogens alter the reproductive hormones and affect female fertility (**Table 2**).

Fetal development

Phytoestrogen exposure altered the normal growth and

Table 2. Effects of Phytoestrogens on female reproductive tract functions.

Animal	Phytoestrogen Compounds	Effects of Phytoestrogens	Refs
Ewes	Clover rich pastures, Subterranean clover	• High rates of infertility and abortion • Reproductive abnormalities in newborn lambs • Failure to conception • Low lambing rates with prolapsed uteri and dystocia • Severe metritis and uterine inertia • Ephemeral labor and fetal death • Reduced ovulation • Ovarian and endometrial cysts • Loss of sexual characteristics	[58,66,67,68]
Cows	Red clover silage, Isoflavones, Alfalfa, Coumestans, Soy	• Cystic ovaries • Behavioral abnormalities, Nymphomania • Irregular estrous, Anestrous, Repeated estrous, False estrous • Abortions • Uterine enlargement, Endometriosis • Swollen vulvae • Increases mean insemination and infertility rates • Inhibits LH-stimulated progesterone (P4) secretion • Fail to ovulate and get pregnant	[59,60,63,64,65]
Ovariectomized heifers	Red clover silage	• Exhibited edema and mucous discharge from the vulva • Fluid accumulation in the uterus • Elongated teats • Presence of milky fluid in the mammary glands	[66]
Captive cheetah	Daidzein, Genistein	• Decreased fertility • Veno-occlusive liver disease	[74]

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Continuation of Table 2.

Beagle dogs	Genistein (Orally)	• Increased uterine weights • Slight decreases in ovarian weights	[50]
Mice	Perinatal genistein	• Accelerated vaginal opening and pubertal onset • Increases the length of the estrous cycle • Accelerates the onset of persistent estrus • Abnormal estrous cycles • Decreases fertility • Delays parturition • Live pups number decreased in adulthood	[77,78,81]
	Neonatal genistein	• Interfere with ovarian differentiation. • Ovarian malformations • Multi-oocyte follicles • Attenuated oocyte cell death • Posteriorized' oviduct • Uterine Cancer	[72,75,76,77]
	Neonatal coumestrol	• Long term reproductive tract abnormalities • Vaginal cysts • Persistent vaginal cornification • Endometrial squamous metaplasia • Absence of corpora lutea • Increased ceroid deposition in the ovaries • Presence of hemorrhagic follicles • Abnormal collagen deposition in the uterine wall	[87]
	Resveratrol, Zearalenone, Bisphenol-A	• Lack of corpora lutea • An extended estrous cycle • Accelerated puberty onset	[84]
Rats	Neonatal genistein	• Ovarian defects • Absence of corpora lutea • Presence of large antral-like follicles with degenerating or no oocytes • Numerous ovarian cysts	[83]
Immature rats	Resveratrol	• Increased uterine weight • Increased Glandular morphogenesis	[86]
Hormonal regulation in mice and rats	Phytoestrogens	• Mimicking E_2 negative feedback • Inhibit the activity of GnRH pulse generator in the hypothalamus • Inhibit serum LH levels in rats via ERβ • Inhibit gonadotropin (LH and FSH) release through ERα • Inhibit oocyte nest breakdown in the ovary • Attenuates cell death during mouse oocyte development • Decrease P_4 and E_2 concentrations in plasma	[72,82,83,84,85,86]

development of animals at various stages. Pre- and neonatal treatment with phytoestrogens altered prepubertal or adult morphology and functions of the uterus, vagina, ovary, breast, pituitary, and hypothalamus [93]. At 1000 mg genistein/kg/day, slight maternal toxicity decreased maternal body weights and food consumption along with increased pup mortality, and reduced pups' body weights and milk uptake were observed in rats. No external malformations were noted in dogs at high doses, but minor visceral and skeletal variations were observed. Besides, maternal body weight and feed consumption were reduced, and the incidence of fetal resorptions increased with a decrease in the number of live fetuses per dam and decreased fetal body weight at the high dietary admix dose of 500 mg/kg/day. An increased non-ossification of certain bones of the paws was observed in fetuses at the same rate, which attributed to the reduction in fetal body weight. As a result, the genistein administration showed fetal toxicity at 500 mg/kg/day [94].

In utero exposure of genistein in the rat and mouse down-regulated several testicular genes such as *Cyp17, Cyp11a*, and *StAR* [95]. Pups from dams treated with high genistein (5,000 µg) had shorter anogenital distances at birth, and female rats in this treatment group had a later onset of the vaginal opening or puberty [96]. Weanling female rats given high dietary coumestrol levels on days 21 to 24 or 22 to 60 caused earlier vaginal opening and irregular vaginal cycles [85]. Coumestrol exposure to neonatal female rats resulted in premature uterine gland development and increased uterine weights on postnatal days 1 to 5, and at later ages, the uterine weights and ER levels were reduced. Also, coumestrol administration on postnatal

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days 10 to 14 inhibited the growth of the uterine gland [97]. In female rats, neonatal exposure to subcutaneous genistein (10μg) elevated pituitary response to the GnRH, whereas, with higher doses of genistein (100μg, 200μg, 500μg or 1000μg) diminished LH secretion at postnatal days 1 to 10 [98]. Oral exposure of genistein to female mice on postnatal days 1 to 5 caused estrogenic responses, including altered ovarian differentiation (multioocyte follicles), delayed vaginal opening, and, subsequently, abnormal adult mouse estrous cycles decreased fertility and delayed parturition [81]. Neonatally, genistein-treated adult females, ovulated spontaneously at about eight weeks of age, continued in a persistent estrous state, and became anovulatory [78]. The adult females' uterus cannot support embryo development, even if blastocysts from untreated control mice were transferred into pseudopregnant genistein-treated mice [99].

Phytoestrogens can cross the blood-brain and placental barrier to a limited extent [12]. Female infants with soy milk formula resulted in abnormal breast milk secretion and withdrawal bleeding. The estrogenic effects from soy were maximum at the vaginal cell walls, then gradually returned to normal. However, vaginal cell reestrogenization was observed at six months of age [100]. These studies suggest that phytoestrogen exposure altered pre-and postnatal fetal reproductive organs' growth and development (**Table 3**).

Influences of phytoestrogens on neuroendocrine level

Reproductive hormones control the reproductive cyclicity of females. Reproductive hormones secretions are controlled by two fundamental mechanisms; positive and negative feedback [45]. GnRH secretion from the hypothalamus is controlled by positive and negative feedback through the kisspeptin-neurokinin-dynorphin neuronal network [101], regulating the gonadotropins; FSH and LH. Elevated progesterone gives strong negative feedback to the hypothalamus, inhibiting GnRH neurons and reducing GnRH synthesis and secretions. This low amount of GnRH is insufficient for follicular growth and development, and adequate estradiol levels prevent cyclicity in females. In contrast, positive feedback activates GnRH neurons, which secretes a large quantity of GnRH through

Table 3. Effects of Phytoestrogens on fetal development.

Model Animal	Phytoestrogen Compounds	Effects of Phytoestrogens	Refs
In general	Phytoestrogens	• Altered prepubertal or adult morphology • Altered functions of the uterus, vagina, ovary, breast, pituitary, and hypothalamus • Cross the placenta and is capable of crossing the blood-brain barrier	[12,93]
Rats	Genistein	• Slight maternal toxicity • Decreased maternal body weights and food consumption • Increased pup mortality, Reduced pup body weights, and milk uptake • Minor visceral and skeletal variations • Fetal resorptions increased • Decreased fetal body weight • Increased non-ossification of certain bones of the paws • Pups had shorter anogenital distances at birth • Delayed onset of vaginal opening or puberty	[94,96]
	Coumestrol	• Weanling female had an earlier vaginal opening and irregular vaginal cycles • Neonatal female rats showed premature uterine gland development and increased uterine weights on postnatal days, along with reduced uterine weights and ER levels • Coumestrol administration on postnatal days 10 to 14 inhibited the growth of the uterine gland	[85,97]
	Genistein (Subcutaneously)	• Female neonatal rats showed an increased pituitary response to gonadotropin-releasing hormone • Higher genistein doses caused a decreased luteinizing hormone secretion on postnatal days 1 to 10	[98]
Rat and Mouse	Genistein (Utero exposure)	• Downregulated the expression of several testicular genes	[95]
Mice (CD -1)	Genistein (Orally, Postnatal exposure)	• Caused estrogenic responses • Altered ovarian differentiation (multioocyte follicles) • Delayed vaginal opening • Abnormal estrous cycles, decreased fertility and delayed parturition in the adult mouse	[81]
	Genistein (Neonatal exposure)	• Adult females ovulate spontaneously up to about eight weeks of age, but then continue in a state of persistent estrous and become anovulatory • The uterus is not competent to support embryo development	[78,99]

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the surge center, stimulating the FSH and LH secretion and triggering the ovulatory cascade [45]. Kisspeptins secreted from hypothalamic neurons in the periventricular, preoptic, and arcuate nuclei act as the possible gatekeepers for GnRH release [102]. Kisspeptin neurons send dendritic arborizations into hypothalamic nuclei, where abundant GnRH cell bodies. Anatomical evidence indicates that kisspeptin acts directly on GnRH neurons, stimulating GnRH secretion [45]. Kisspeptin also acts as an essential regulator for sexual differentiation of the brain, the timing of puberty, and adult regulation of gonadotropin secretion by gonadal steroids [103]. So, kisspeptin neurons may be stimulated by positive and negative feedback by gonadal steroids that mediate GnRH secretion by GnRH neurons [45].

Phytoestrogens exert their effects on reproductive processes at different regulatory levels. In the ruminants, numerous studies were conducted to study the direct impact of phytoestrogens on the CNS, pituitary gland, and hypothalamus. As phytoestrogens bind with the estradiol receptor in the hypothalamus and pituitary, the estradiol feedback mechanism for LH synthesis and secretions were interfered in ewe [104]. A high concentration of coumestrol diet reduced LH pulses amplitude significantly during the breeding season, but no effect was observed in the seasonal anestrous in ovariectomized ewes [105]. Genistein might also effectively modulate LH and prolactin secretion in ovariectomized ewes by acting within the CNS [106]. Genistein infusion to the brain's third ventricle altered LH-producing cell activity in the anestrus season of the ewes' pituitary glands. Due to genistein exposure, LHβ-positive cells showed a decreasing percentage and density of immune-reactivity, but genistein exposure stimulated the percentage and integral density of LHβmRNA-expressing cells. Genistein also stimulated the expression of ERα in the LHβ-expressing cells by decreasing the pool of secretory granules stored in the LH-producing cells, which augmented the synthesis of β subunit for LH [107]. Intracerebroventricularly genistein administration in ewes showed that this plant-derived isoflavone, as 17β-estradiol can be a stimulator of GH secretion resulting in diminishing storage of GH in the pituitary somatotrophs in ewes and it can exert its effect at the level of the CNS [108]. Endogenous estrogen production in the ovary was decreased due to phytoestrogen presence, leading to disturbances in the immune system, follicles development and estrous cycle [109]. Animals fed with a soy diet exhibited a higher concentration of active metabolites of phytoestrogens in the CL tissues than the animals on a standard fodder diet. Pituitary LH and ovarian PGE2 are known to induce P_4 secretion in mammalian ovaries. Cows fed with phytoestrogens and their active metabolites had lower P_4 secretion by inhibiting LH and PGE2 [69]. Intestrignly, phytoestrogen compounds (such as equol and para-ethyl-phenol) increased PGF2α secretion resulting in an increased E_2 and testosterone (T) production during the late luteal phase, leading to termination of CL function and abortion during early pregnancy [110]. Due to exposure to phytoestrogens and their metabolites, PGF2α and PGE2 productions were significantly increased, where the PGF2α level was higher than PGE2 [68]. P_4 biosynthesis is also stimulated by a lower PGF2α/PGE2 ratio [111]. For the establishment of pregnancy, the PGF2α/PGE2 ratio should be lower for preparing the uterus for embryo implantation by relaxing the blood vessels and increasing blood flow in the uterus. Soybean stimulated PGF2α secretion in the luteal phase, which negatively affects the embryonic development in cows [112]. Early embryo mortality or abortion depends on the stimulation intensity between PGF2α and PGE2 production in the bovine endometrial tissue [68]. During luteolysis and ovulation, phytoestrogen and their metabolites possibly act like endogenous estrogens, which may highly stimulate the mechanism and return the cow to cyclicity after labor [68]. Several genes are responsible for synthesizing the oxytocin precursor, neurophysin-I/OT, and post-translation synthesis of oxytocin, peptidyl glycineα amidating monooxygenase or PGA granulosa and luteal cells are altered due to phytoestrogens such as coumestrol, daidzein, and genistein. Premature luteolysis and persistent corpus luteum formation in cattle may result from the stimulation of oxytocin in ovarian follicles and corpora lutea by phytoestrogens [113]. These studies supported the hypothesis that phytoestrogens results in hormonal imbalances and causing pregnancy failure in females.

Cellular and enzymatic mechanisms of phytoestrogens

It is well known that phytoestrogens regulate PG synthesis in a cell-specific manner in stromal cells by increasing PG without altering PGF2α/PGE2 ratio. They direct the biosynthetic pathway toward PGF2α in epithelial cells via stimulation of PGFS expression [68,114]. Phytoestrogens inhibit (H3)- E2 and (H3)-Organon binding to their respective receptors, but the relative affinities of E_2 are higher than the affinity of (H3)-E2 and (H3)-Organon [33,109,115]. In humans and cows, phytoestrogens have only 0.1% to 1% affinities for estrogen receptors than circulating estrogen [116]. Through an estrogen-receptor-dependent genomic pathway, phytoestrogens increased PGF2α and PGE2 in the bovine endometrial epithelial, stromal, and CL cells. Endometrial epithelial cells showed stimulative effects of equol and para-ethyl-phenol on PGF2α synthase-like 2 (*PGFSL2*) gene and protein levels [68,117]. Genistein exposure inhibited MAP kinase activity and PLD activity in vascular smooth muscle cells [118] and PLC-dependent intracellular calcium release [119]. Bovine endometrial epithelial and stromal cells viability were also reduced due to exposure to phytoestrogens and their metabolites [114]. Estrogens also stimulated epithelial and endothelial cell growth and proliferation in the female reproductive tract [122]. Detrimental effects of phytoestrogens on reproductive processes may depend on various intracellular and receptor-mediated pathways activation along with the activation of multiple enzymes related to arachidonic acid metabolism [114].

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Conclusions

Environmental phytoestrogens have a considerable impact on the growth and development of the male and female genital system and subsequent fertility. Several studies using a ruminant model showed that phytoestrogens exposure has significant consequences for reproductive health. The animal data revealed that the timing of exposure to such compounds is crucial, with neonatal exposure having the most pronounced effects. Exposure of phytoestrogens to neonates and adults is of great concern as it alters hormonal regulation and metabolism in the body and can leave prolonged effects. The biological activity of phytoestrogen depends on multiple factors, such as the chemical form of the phytoestrogen, route of administration, metabolism, endogenous estrogenic status, age, and exposure level. These parameters are crucial for determining phytoestrogen-induced effects on the host. Further studies are required at the genetic, epigenetic, and molecular levels to understand the adverse effects of different phytoestrogens compounds and relative health hazards in animals and humans. These findings can be instrumental in formulating interventional strategies depending on the animal species, types of phytoestrogens consumed, and duration of exposure.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	MRA	CNL	BM
Research concept and design	--	--	✓
Collection and/or assembly of data	✓	--	✓
Data analysis and interpretation	✓	--	✓
Writing the article	✓	✓	✓
Critical revision of the article	✓	✓	✓
Final approval of article	✓	✓	✓
Statistical analysis	--	--	--

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