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Effect of Phytoestrogens on Some Reproductive Physiology and Performance

Zhina Abbas Mohammed* and Sarood Samal Shawkat

Department of Animal Science, College of Agricultural Engineering Sciences, University of Sulaimani, Iraq

***Corresponding author:** Zhina Abbas Mohammed, Department of Animal Science, College of Agricultural Engineering Sciences, University of Sulaimani, Sulaimaini, Iraq

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ABSTRACT

The utilization of legumes in animal diets and the adoption of vegetarian diets in certain human populations have led to a rise in the worldwide consumption of phytoestrogens. Consequently, the effects of these compounds have also increased in both animals and humans. Phytoestrogens are widely found in various plants and animal feed, and mainly have adverse effects on the reproductive system of most animal species. It is possible for some phytoestrogens to act as either estrogenic agonists or antagonists. They may have a variety of effects, such as infertility and behavioral changes in animals, or an enhanced estrogenic response that results in more secretions in the reproductive system. Because of this, many phytoestrogens are now recognized as endocrine disruptors, meaning they may prevent the body's natural hormones—which are essential for reproductive processes-from being produced, released, moving, attaching, functioning, or being removed. The impact of phytoestrogens primarily relies on the particular variety, botanical species, and quantity consumed. Recently, studies have been conducted to investigate the additional impacts that phytoestrogens may have on the metabolism, immune capacity, and growth and performance of grazing livestock. Phytoestrogens, while offering potential health advantages, also exert detrimental impacts on the reproductive well-being of both males and females. Phytoestrogens bind to estrogen receptors (ER), interfere with the hormonal regulation of the reproductive organs, and increase the chances of infertility, irregular estrus cycles, and anestrous. Phytoestrogens have been linked to a number of positive health outcomes. These outcomes include a lower likelihood of developing osteoporosis and menopausal symptoms like hot flashes, as well as a decreased risk of cardiovascular disease, obesity, metabolic syndrome, type 2 diabetes, and brain function issues.

Introduction

Non-steroidal substances originating from plants are called phytoestrogens. These substances are structurally comparable to natural estrogens, particularly 17β-estradiol, which allows them to bind to estrogen receptors and subsequently have biological effects that are evident [1]. The roots "photo" (referring to plants), "estrous" (referring to estrous), and "gen" (referring to generation) are combined to give them their name. Plant-based feeds are acknowledged as a plentiful source of phytoestrogens (PEs), which are nonsteroidal polyphenolic compounds produced through plant metabolism and possess a distinct conformational structure. Phytoestrogens have the ability to imitate the effects of estradiol (E2), but it should be noted that their effects may not be exactly the same. Phytoestrogens can exhibit either estrogenic or antiestrogen effects [2]. The existence of these compounds engenders a rivalry with naturally existing steroids. The ratio of phytoestrogen to estrogen influences the relative levels of estrogenic and antiestrogen activity [3]. This could potentially elucidate the reason why the estrogenic impacts of phytoestrogens are more discernible in livestock, as their estradiol plasma concentrations are comparatively low (15 pg/ml). Plant-based feeds are recognized as a plentiful source of phytoestrogens (PEs), which are nonsteroidal polyphenolic compounds produced by plants. These compounds exhibit a comparable molecular arrangement to 17-β estradiol (E2) as described by Pérez-Rivero et al. [4] and Gioia, et al. [5].

When animals consume them, these substances can selectively modify estrogen receptors (ERs) and function as endocrine disruptors, either mimicking or blocking their activity. The specific effect depends on the amount consumed (Gioia, et al. [5,6]). Hence, they

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have the potential to disrupt the synthesis, secretion, conveyance, and degradation of reproductive hormones, both in the early stages of growth and in later life. The sources cited are Adams [6] and Whitten and Patisaul [7]. The levels of phytoestrogens in different foods can vary, and this variation can be substantial even among foods in the same category, such as soy beverages and tofu. The variability in phytoestrogen levels can be ascribed to the processing techniques employed and the particular variety of soybeans used. Legumes, particularly soybeans, whole grain cereals, and specific seeds, possess substantial quantities of phytoestrogens. The four main classifications of phytoestrogens consist of isoflavones (such as genistein, daidzein, glicetin, formononetin, biochanin A, and equal), flavones (including quercetin and campherol), coumestans (specifically cumestrol), and lignans (such as enter lactone and enter diol) (Strauss et al. [8]). Furthermore, plants or their seeds contain stilbenes, such as resveratrol, and mycotoxins, specifically zearalenol α and β. It is important to mention that specific fungi can also produce these compounds (Moutsatsou, [9]).

Effect of Phytoestrogens on Female Reproductive

The use of pasture legumes in animal husbandry has significantly increased worldwide (Rachuonyo, et al. [10,11]). It has been shown that phytoestrogens may lead to problems in sheep and cow reproduction. The potential for phytoestrogens to alter the endocrine system was first noticed in Australia. Piotrowska, et al. [12] discovered that ewes who fed on pastures with high clover content had an increased risk of infertility, abortion, and abnormalities in the reproductive system in their young lambs. Long-term soy-based diet intake reduces progesterone (P4) production triggered by leptin (LH) and has a considerable impact on average rates of insemination and infertility (Woclawek-Potocka, et al. [13]). Because they do not ovulate, cows are unable to get pregnant (Piotrowska, et al. [12]). The prevalence of flavone-induced infertility is rising, even in the absence of symptoms. Only the presence of phytoestrogens in the food or their impact on the animal's reproductive efficiency and health may be used to diagnose this illness (Adams, [6]). Furthermore, long-term soy-containing diet intake by cows has deleterious effects during the first trimester of pregnancy, leading to abortions during the first trimester.

According to the theory, flavone, equal, and para-ethyl-phenol-three active metabolites-may be responsible for the effects. This is because, in contrast to the later stages of pregnancy and the estrous cycle, their levels are greater in the early stages of pregnancy (Woclawek-Potocka, et al. [14]). Pigs fed grain show signs of hyperestrogenism and have trouble reproducing. The invasion of the grains by saprophytic fungus, mostly Fusarium, is the cause of the issues. In Australia and New Zealand, these cereals are thought to be the main contributors of pasture pollution. It has been shown that zearalenone, a fungus molecule, has a strong estrogenic activity and is a major contributor to these problems. This compound is produced in the ruminant and exhibits a notable estrogen-like effect on livestock, similar to its metabolites α- and β-zearalenol. Reed, et al. [15] reported that Zearalenone concentrations in the nation of New Zealand typically range from 50 to 500 μg/100 g throughout the fall period. Because the mycoestrogen complex causes the organism to produce excessive amounts of estrogen, it reduces infertility by delaying conception and lengthening the length of the reproductive cycle. Furthermore, cortisol prolongs the duration of estrous in female sheep. However, it fails to have any impact on the rate of fertilization or the rate of embryo loss (Nynca, et al. [16]).

Effect of Phytoestrogens on Male Reproductive

Here is an increase in interest in studying the impact of estrogen-like substances on the fertility of males. This is because the research shows the significant role that estrogen have in the male reproductive system (Rochira, et al. [17]). Although full information is lacking, it is evident that phytoestrogens may also disrupt reproduction in males. When cattle eat feed with high cholesterol, glandular metaplasia occurs in the prostate and bulbourethral glands (Lenis, et al. [18]). The condition known as which refers to the growth of the breast tissue in males, or agalactorrhea, a disorder characterized by the abnormal production of breast milk, may be caused by this illness (Romero, et al. [19]). Genistein, also may affect the signal transmission route in frozen bull Spermatozoa, without relying on proteins osine activation. The process in issue is responsible for inducing sperm stimulation, triggering an acrosome reaction, and facilitating sperm attachment to the pellucid region.

Therefore, there is a decrease of 40-50% in acrosome reaction (Menzel, et al. [20]). There are worries regarding the potential hazards of estrogen-like substances to humans and livestock due to their parallels to the effects of DDT on wild bird populations. Consuming a diet rich in phytoestrogens could lower the levels of ERα and AR in the cauda epididymis, enhance lipid oxidation in epididymis sperm, impede the production of sperm, and induce germline cell division (Assinder, et al. [21]). The disturbance of the hormonal regulation of the epididymis is likely to have an influence on sperm quality and, as a consequence, fertility (Glover, et al. [22]). On the other side, persistent testosterone use in conjunction with vinclozoline, a hormone-disrupting fungicide, has been demonstrated to reduce sperm count and motility, reduce the amount of offspring, and increase fetal loss after insertion (Eustache, et al. [23]).

Effect of Phytoestrogens on Metabolism and Metabolic

According to Njåstad, et al. [24], phytoestrogens, often found as glycosides in plants, do not exhibit estrogenic properties. Phytoestrogens undergo a variety of chemical changes after intake in animals, including demethylation, methylation, hydroxylation, chlorination, iodination, and nitrification. Phytoestrogens or their byproducts are mostly found in plasma in a variety of conjugates or sulfa-conjugates (Höjer, et al. [25]). Through metabolism, they undergo in vivo con-

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version into unconjugated forms that are more estrogenically active (Höjer, et al. [25]). Sheep typically exhibit more vigorous mating behavior than cattle in most areas of the digestive system, with the exception of the small intestine (Brito, et al. [26]). The liver and kidneys engage in the metabolic process of conjugating unbound phytoestrogens with glucuronic acids and sulfuric acid (Hashem, et al. [27]), and subsequently reassembling them (Sirtori, et al. [28]). The metabolites undergo enterohepatic recirculation after passing through the rumen (Třináctý, et al. [29]). The presence of phytoestrogens in the milk of lactating ruminants is a result of the consumption of feed that contains estrogenic compounds. The elimination of these phytoestrogens primarily takes place via urine in the form of conjugated compounds, and via faces as unconjugated compounds (Höjer, et al. [25]). Phytoestrogens indirectly decrease the level of biologically active estradiol in the blood by stimulating the production of steroid hormone binding globulin (SHBG) in the liver. Flavones exhibit slight antiestrogen effects when estrogen is not present, and potent antiestrogen effects when estrogen is present (Burton, et al. [30]).

Effect of Phytoestrogens on Growth and Performance

Certain phytoestrogens have been discovered to possess advantageous characteristics, such as the ability to enhance growth rate and promote weight gain in livestock. Studies have observed that a higher amount of genistein, as opposed to formononetin, leads to an increase in the rate at which ewes and lambs gain weight when they are fed subterranean clover (Pace, et al. [31]). Furthermore, a correlation was found among this occurrence with an elevated assimilation of metabolizable proteins. As an investigation conducted by Pace, et al. [31], it was shown that the treated ewes and lambs exhibited a significant increase as average daily gain (ADG) of 26.3% and 31.7% correspondingly following an 8-week feeding period, as comparison to the untreated group which fed Italian rye grass. The carcass weight have been determined to be 18.7% higher than those of the control group. The investigation done by Pace, et al. [31] found that rats that were exposed to the medication showed increased levels of internal and total body fat, increased length and weight of leg bones, and faster maturity. The present study suggests that some phytoestrogens, such as genistein and have the potential to act as powerful androgen agents. Nevertheless, the apparent impact might be obscured as a result of the incorporation of additional sustenance.

A substance called a the flavone molecule, enhances the decomposition of dietary proteins and stimulates the release developmental hormone. Adolescent adult cattle benefit from an enhanced physiological state as a result, resulting in heightened production (Zhao, et al. [32]). Runyan, et al. [33] examined the potential effects of include soybean meal, as an alternative protein the source, in a long-term diet of bulls on their reproductive capacity. Bull calves had a higher average daily increase in weight (ADG) when fed a diet containing 10% soybean meal, compared to their peers of the same age group who were given cotton seeds instead of soybean meal. The study done by Liang, et al. [34] has shown that the inclusion of daidzein into the feed of beef cattle enhances rumen fermentation. Zhao, et al. [35] discovered that a substance called unlike zearalanol, may increase the amount of intramuscular fat and marbling score in steers. The elevation in the production of lipids is attributed to the estrogenic characteristics of daidzein, which hinders the degradation of lipids in the liver, thereby leading to elevated levels of unbound fatty acids in the circulation (Liang, et al. [34]).

Effect of Phytoestrogens on Neuroendocrine Level

Hormones related to reproduction regulate the female ovarian cycle. The regulation of the secretion of hormones throughout reproductive is governed by several fundamental mechanisms: positive and negative feedback (Senger, [36]). The secretion of GnRH in the brain's hypothalamus is regulated by a complex network of kisspeptin-neurokinin-dimorphic neurons that involves both positive and negative feedback mechanisms. The system in question plays a crucial role in the regulation of gonadotropin stages, namely follicle-stimulating hormone (FSH) and luteinizing hormone, also known as (LH). Elevated progesterone levels have a significant inhibitory effect on the brain's hypothalamus, leading to a decrease in the rate of firing of neurons that produce GnRH, in addition to a reduction in GnRH synthesis and emission. Insufficient GnRH hampers the growth and maturity of follicles, where as ample estradiol prevents the creation of cyclical patterns in females. Conversely, favourable feedback stimulates GnRH cells, leading for the secretion of a substantial quantity of GnRH (Marques, et al. [37]). Kisspeptins, that are synthesised by neurons in the hypothalamus in the periventricular, preoptic, and arcuate nuclei, has the ability to control the production of GnRH (Roa, et al. [38]).

Kisspeptin cells project dendrite filament into hypothalamus regions densely populated with GnRH body cells. Based on anatomic findings, kisspeptin directly affects GnRH neurons by stimulating the release of GnRH (Senger, [36]). Kisspeptin possesses a crucial function in regulating cerebral sexually differentiating themselves, the timing of puberty, and the generation of gonadotropins through the gonads (Roa, et al. [39]). Kisspeptin cells may be activated by both positive and negative feedback from gonadal steroids, which control the generation of GnRH by Fsh-producing neurons (Senger, [36]). The compounds found in plants decreased the production of natural estrogen inside the ovary, leading to disturbances in the immunological framework, proliferation of ovarian follicles, and the estrous cycle (Rosselli, et al. [40]). Those that were provided with a diet composed of soy exhibited higher levels of the active metabolites of phytoestrogens in their CL tissues compared to animals that received a typical hay diet. The process by which pituitary luteinizing hormone (LH) and ovarian prostaglandin E2 (PGE2) stimulate the generation of progesterone (P4) in the mammal ovary is well comprehended. Administering phytoestrogens and their metabolites that are active to cows resulted in a decrease in P4 production by inhibiting the synthesis of LH and PGE2 (Piotrowska, et al. [12]).

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Effect of Phytoestrogens on Various Regulatory Levels

Phytoestrogens have the potential to disrupt reproductive processes in several regulation stages (Benassayag, et al. [41]). Various scholarly investigations have employed the ruminant model to precisely examine the instantaneous effects of phytoestrogens on the central nervous system (CNS), encompassing the region of the hypothalamus and brain. Romanowicz, et al. [42] examined the interplay between phytoestrogens and the estradiol receptors in the pituitary gland and hypothalamus. The study participants also identified phytoestrogens, which might disrupt the estradiol cycle responsible for stimulating the synthesis of luteinizing hormone (LH) in female sheep (Polkowska, et al. [43]). Nevertheless, the impact of consuming phytoestrogens from food on LH production appears to depend on the specific phytoestrogen, as well as the individual's reproductive condition and the time of year. Female sheep who had surgical removal from their ovary and were given a diet rich in coumetarol saw a notable reduction in the intensity of LH pulses across the entire menstrual season. Nevertheless, this wasn't the case during the period of anestrus (Polkowska, et al. [43]). Romanowicz, et al. [42] investigated the potential impact of a certain factor on the production of LH and prolactin (PRL) in sheep that had their ovaries removed, specifically during the period of annual anestrus. Following an extended period of administering genistein directly into the third ventricle, there was a reduction in the amount of LH present in the bloodstream, as well as a decrease in the frequency of LH pulses.

Moreover, the administration of testosterone by injection led to a significant increase in plasma levels of PRL both during and after the infusion, in comparison to the group that did not receive any treatment. According to Romanowicz, et al. [42], research indicates that genistein has the potential to regulate the release of LH and PRL in ovariectomized ewes by influencing the central nervous system. This study investigated the impact of phytoestrogens on the synthesis of the bovine endometrium, the inner lining of the uterus in cows (Wocławek-Potocka, et al. [13]). The in vitro tests demonstrated that the phytoestrogen metabolites equol and p-ethyl-phenol exhibited much more disruptive effects compared to the original phytoestrogens. Wocławek-Potocka, et al. [14] found that metabolites exhibit a stronger binding to receptors for oestrogen compared to the initial phytoestrogens, leading to enhanced efficacy. The hypothesis is supported by the findings of Benassayag, et al. [41], who revealed that phytoestrogen compounds possess a potency that is around 100-150% higher compared to that of naturally occurring estrogens.

Effect of Phytoestrogens on Menopausal Symptoms

Multiple systematic reviews looked at the impact of phytoestrogens, namely soy-based flavone extracts or supplements, on problems experienced during menopause. According to the findings, there were instances when both the intensity and frequency of hot flashes have reduced (Taku, et al. [44,45]). However, in other situations, the data was equivocal or gave little proof of a decrease in the frequency or intensity of hot flashes (Eden, et al. [46]; Lethaby et al., 2013). Taku, et al. [47] found that the influence on the density of bone minerals in the vertebral column was different, but there was little effect seen in the femoral neck, hip total, or trochanter. In addition, there were no preventive interventions implemented to mitigate the possibility of bone fractures (Kreijkamp-Kaspers, et al. [48,49]). The European Food Safety Authority (EFSA) evaluated the therapeutic advantages of soy flavones in menopausal women, namely their capacity to alleviate symptoms of cardiovascular insufficiency and preserve the density of bones (EFSA NDA Panel, [50]).

The available data were inadequate to demonstrate a link between intake of soy flavones and the maintenance of bone mineral density. Furthermore, there was also no apparent correlation between the decrease in symptoms of vasomotor dysfunction related to menopause with the use of soy is flavones. EFSA conducted a comprehensive assessment of 14 intervention research studies, each with a duration of over a year, that examined the impact of is flavones derived from soybeans on the bone mineral density of postmenopausal women. Among all the performed investigations, just two demonstrated a discernible effect of soy flavones are on bone mineral density and indicators of bone formation or degradation. The aforementioned effects were found when every day of 54 mg was administered, as recorded by (Marini, et al. [51]).

Effect of Phytoestrogens on Brain Function

The rationale for doing these tests lies within the substantial influence that estrogens exert on brain health. The hypothalamus-pituitary-gonadal axis regulates the synthesis of estrogen in the cerebral cortex, which is additionally affected by estrogens. Moreover, estradiol plays a vital role in the neurobiology of ageing, since changes of both hormonal and brain functioning are intricately linked via elaborate mechanisms of feedback (Morrison, et al. [52]). The current consensus is lacking regarding the impact of estrogen therapy on brain health, as it remains uncertain whether it has a positive or negative effect. The variations in observations can be attributed to the initiation time of estrogen therapy, the neurological condition of the brain at the beginning of therapy, and the specific method of therapy employed (Brinton, [53]).

According to a review of the literature on the neuroprotective properties of soy phytoestrogens, although studies on animals and in cells have suggested that soy phytoestrogens may have a positive effect on the brain, human observational studies and clinical trials have not yielded clear-cut results (Soni, et al. [54]). The beneficial effects of phytoestrogens, like treatment with estrogen, may be affected by several situations. Several factors, including duration of use, postmenopausal status, age, gender, ethnicity, and the specific cognitive assessment employed, have a major impact on cognitive performance. The research population is characterized by a key feature, that is the metabolism ability to create equol. This ability varies across Asian and non-Asian groups and tends to decrease with aging (Soni, et al. [54]).

Conclusion

A growing number of phytoestrogens, including coumestanes, stilbenes, and flavones, have been discovered in the natural environment. As a result, the number of phytoestrogens is growing, and their biological significance has yet to be determined. The choice of experimental approach is critical in determining phytochemicals' estrogenic impact. The estrogenic effects of phytoestrogens were first studied in vitro. Nonetheless, animal models are preferable for accurately assessing these drugs' genuine estrogenic capability. Several variables impact phytoestrogen biological activity, including their chemical structure, mode of administration, metabolism, the individual's intrinsic estrogenic status, age, and the length and intensity of exposure. Plant chemicals known as phytoestrogens have received interest as a secondary defense mechanism. They have been investigated for their possible biological effects on animals, specifically on reproduction, metabolism, and immunological function, among other things. The presence of phytoestrogens in neonates and adults is reason for worry since they may disrupt the body's hormonal control and metabolism, perhaps causing long-term damage. The effectiveness of phytoestrogen is influenced by many aspects, including its chemical makeup, administration mechanism, metabolic processes, natural estrogen levels, age, and exposure level. Phytoestrogens are being more recognized as significant medicinal agents. Potential benefits include a lower risk of developing menopausal symptoms, cardiovascular illness, breast cancer, as well as other types of cancer such as prostate cancer, bowel cancer, uterine cancer, and different cognitive impairments [55].

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