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Review

Effects of phytogenic feed additives on the reproductive performance of animals

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ABSTRACT

The reproductive performance of ruminants is economically significant, and its improvement is a primary goal of the livestock industry to ensure its sustainability. Several approaches have been developed to use phytogenics as feed additives for several proposes, such as reducing methane emissions, and as an alternative to antibiotics. Phytogenics have potent antioxidant, anti-inflammatory, immunomodulatory, and metabolism-regulatory properties, and they are present at high levels in animal feeds. This current review considers the potential use of medicinal herbs on the reproductive performance of animals. The influence of diet on the fertility complications commonly noted in ruminants is of global interest. Although the effects of phytogenics on ruminant digestion and absorption are well-explored, their impact on reproductive performance remains poorly investigated. This review focuses on the influence of phytogenics on semen quality, hormonal profiles, and hematobiochemical indices in male ruminants. Based on available data, phytogenics are perceived to improve oocyte quality, reproductive performance, and pregnancy. However, further more comprehensive research on the benefits and potential hazards of the use of phytogenics is required to improve reproductive performance in ruminants.

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1. Introduction

Using antibiotics as feed additives in ruminant diets during the reproductive period enhances reproductive efficiency and improves nutrient utilization, resulting in measurable health benefits (Petersson-Wolfe et al., 2007); however, their application in ruminant diets is controversial because of the risk of their transmission into meat and milk as well as the antimicrobial resistance induced by the misuse of antibiotics, focusing the concern of new alternatives to antibiotics in the field of animal nutrition (Makkar et al., 2007; Cieslak et al., 2013).

These concerns have inspired the search for alternative natural feed additives. Considering this, phytogenics, such as spices and herbs, which have phytonutrients, phytochemicals, and essential oils, have been developed as alternative growth promoters and antimicrobial agents to improve the quality of animal products (Abdelnour et al., 2018). Additionally, phytogenic feed additives have been used to improve the reproductive performance of farm animals, and there has been a growing interest in the use of phytogenics to enhance the reproductive efficiency of livestock because of their antioxidant and anti-inflammatory properties and lower toxicity than synthetic antioxidants.

Studies have shown that extracts from herbs or phytochemical compounds have beneficial effects on fresh semen and post/thawed semen (Ahmed et al., 2019, 2020; Nikhade et al., 2019; Azimi et al., 2020). However, their effects on reproductive performance require further investigation to achieve potential improvements and reduce hazardous risk (Khalifa et al., 2014; Hashem et al., 2018a, 2018b; Ahmed et al., 2020; Merati & Farshad, 2020).

The use of phytogenic feed additives with antioxidants to enhance the outcomes of *in vitro* fertilization has been extensively documented in different species for reducing the generation of oxidative stress in the medium (Ahmed et al., 2019, 2020; Azimi et al., 2020).

Additionally, as reproductive performance is considered the primary measure of success of livestock production systems (Abdelnour et al., 2020), the addition of some phytogenics to ruminant diets could enhance reproductive efficiency (Ahmed et al., 2020). Other studies have reported that certain phytogenics have estrogenic effects and therefore might cause an imbalance in hormonal regulation in animals (Hashem et al., 2018a; Hashem et al., 2018b).

This review article reviews the scientific literature on the effects of phytogenic feed additives on the reproductive performance of ruminants. This review provides an overview of phytogenics and their effects on the sexual behavior, hormonal profiles, fertility rates, conception rates, and sperm quality of the semen of livestock.

2. Mode of action of phytogenic feed additives

The inclusion of phytogenics in livestock diets can enhance animal performance and improve reproductive efficiency. The antioxidant effect of phytogenics such as herbs and their extracts in the diets of ruminants as photobiotic is another biological activity of great attention. Reports provide evidence of the capability of phytogenics to neutralize oxidation, and they can be critical for mitigating some environmental impacts (Abd El-Hack & Alagawany, 2015; Hussein et al., 2019; Abd El-Hack et al., 2020).

Additionally, the antioxidant properties of phytogenics are based on their ability to provide electrons or hydrogen ions and delocalize unpaired electrons within the phenolic aroma ring of their structure and are the central mechanisms of defense of biological molecules against oxidation (Abd El-Hack et al., 2015, 2016, 2017).

Despite this, there is very limited published data on the impacts of using phytogenics as feed additives to enhance the reproductive performance of ruminants. According to Abd El-Hack et al. (2020) and Merati & Farshad (2020), phytogenic feed additives, such as herbs and their extracts, that have potential antioxidant effects, mainly products derived from ginger, *Echinacea* extracts, green tea, purslane extracts, *Moringa oleifera*, honey bell, rosemary, and yucca, owing to their phenolic compounds (Khalifa et al., 2014; Shedeed et al., 2019; Merati & Farshad, 2020).

Several active compounds have been isolated from these herbs, such as quercetin, carvacrol, menthol, thymol, rosmarinic acid, eugenol, rosmarol, and propolis, which have powerful antioxidant, anti-inflammatory, and antibacterial effects (Ahmed et al., 2019, 2020; Abd El-Hack et al., 2020; Azimi et al., 2020). Interest from the scientific community has been shifted to identify new, efficient, natural dietary feed additives for livestock to improve reproductive performance and boost the health and function of intestinal tract. The dependability of phytogenic feed additives as an alternative in agro-food systems needs to be proven.

3. Effects of phytogenic feed additives on male reproductive functions

For a long time, phytogenics have been widely used for promoting fertility by improving sexual activity through increasing the synthesis of steroidogenesis and hence testosterone secretion. Hashem et al. (2013) detected that the dietary administration of propolis (150 mg/kg diet) resulted in specific enhancements in sexual activity, spermatogenesis, and the antioxidant status of rabbit bucks during hot summer conditions. A part of this effect was attributed to high levels of high-density lipoprotein, which plays several pivotal biological roles by enabling the transportation of hydrophobic lipid molecules, such as triglycerides and cholesterol, within the water-based bloodstream, transporting cholesterol into steroidogenic tissues, such as the testes, ovaries and adrenal glands; and eliminating the excess molecules of low-density lipoprotein via the liver (Hashem et al., 2013).

The oral administration of *M. oleifera* leaf extract (40 mg/kg of body weight) in rams increased the semen volume, sperm concentration, sperms motility, viability index, membrane integrity, activities of seminal plasma catalase, superoxide dismutase, glutathione reductase and peroxidase, total antioxidant capacity, ascorbic acid, and some metabolite enzymes, such as alkaline phosphatase and acid phosphatase (El-Desoky et al., 2017). *M. oleifera* has a wide range of antioxidant and anti-inflammatory polyphenols that can improve the success of reproductive events (El-Desoky et al., 2017).

Pamungkas et al. (2019) indicated that bulls fed with herbs for 3 months exhibited improved volume, concentration, viability, and motility of sperm. Additionally, boars fed ginseng root were reported to have significantly increased sperm concentration, significantly reduced lipid peroxidation, and improved levels of antioxidants enzymes, such as glutathione peroxidase, and antioxidant levels in their seminal plasma (Yun et al., 2016).

In comparison, the administration of ginger extracts induced higher ($P < 0.05$) levels of testosterone and sperm concentrations in boars (Yun et al., 2016). The higher levels of testosterone detected in the ginger-treated group could be owing to a decline in the amounts of oxidative stress, which inhibits steroidogenic enzymes for testosterone synthesis (Yun et al., 2016). Another possible explanation is that ginger extracts could directly affect Leydig cells to stimulate the synthesis of testosterone. This improvement in testosterone secretion caused by administering ginger extracts might be related to the bioactive compounds of ginger, such as ginsenosides, which catalyze the biosynthesis of androgens in the testes (Salvati et al., 1996).

Recently, El-Azrak et al. (2017) reported that rams that received 1.5 ml of cinnamon oil by oral administration for 8 weeks had an increased libido and improved semen quality. Additionally, supplementation of green tea extract, which is rich in catechins, at a dose of 1% significantly enhanced the *in vivo* fertility rate of buffalo spermatozoa by 34.21% compared with the control treatment (Ahmed et al., 2020).

It has also been documented that phytogenic feed additives included in semen extender improved the cleavage rate and formation of morula and blastocyst in rodents after *in vitro* fertilization (IVF) (Ardeshirnia et al., 2017) and the *in vivo* fertility rate in buffalo (Ahmed et al., 2019). Adding 150 or 200 μM of quercetin to semen extender before freezing has also been found to be beneficial in buffalo, with 31.8% and 39% higher *in vivo* fertility success, respectively, than the control treatment (Ahmed et al., 2019). Overall, it is evident that phytogenic compounds with antioxidant activity can induce substantial improvements in male reproductive performance when used at optimum doses.

The effects of phytogenic feed additives on male reproductive function are illustrated in Fig. 1.

4. Effects of phytogenic feed additives on female reproductive functions

The critical regulators of ovarian activity are female steroid hormones, including progesterone, *P*4, oestradiol-17β, and E2 hormones, which play substantial roles in the development and differentiation of reproductive organs, sexual behavior, and fertility. Shedeed et al. (2019) reported that pregnant ewes fed basal diets with 5 g of propolis showed a significant increase in leucocytes and decrease in erythrocytes, along with mean corpuscular hemoglobin, compared with the control.

Moreover, they also detected an increase ($P < 0.05$) in the plasma immunoglobulin A in response to propolis supplementation. Simultaneously, nitric oxide, hydrogen peroxide, and superoxide dismutase decreased ($P < 0.01$) in ewes that received propolis compared with the control (Shedeed et al., 2019). *M. oleifera* leaf meal supplemented to the basal diet of lactating dairy cow at 60 g of *M. oleifera*/cow/day significantly increased the serum total antioxidant capacity, total protein, and IgG and reduced the levels of non-esterified fatty acids (Kekana et al., 2019). Further, the inclusion of yucca in the diets of cattle (Cheeke, 2000) and dairy goats (Khalifa et al., 2014) enhanced the conception rates, shortened the estrus cycle, and increased the fertility and kidding rates in goats (Khalifa et al., 2014).

Yucca has high levels of phenolic compounds and minerals, such as calcium, and after ingestion, it can reduce the plasma levels of urea in goats (Khalifa et al., 2014). Subclinical endometritis is a common cause of subfertility and infertility in highly productive dairy cattle, and it delays the onset of ovarian cyclic activity after parturition, prolonging the luteal stage and decreasing the fertility rate (Sheldon et al., 2009).

Nikhade et al. (2019) assessed the efficacy of herbal extracts in treating subclinical endometritis disorder in cows by intrauterine administration of 25 ml sterile hydromethanolic extract of *Azadirachta indica* or 20 ml (10 mg/ml) sterile hydromethanolic leaf extract of *Achyranthes aspera* (200 mg) for 3 consecutive days. Their findings indicated that the curative efficacy of *A. aspera* was greater than that of *A. indica*, followed by no treatment. The conception rates were 50% and 40% for *A. indica* and *A. aspera*,

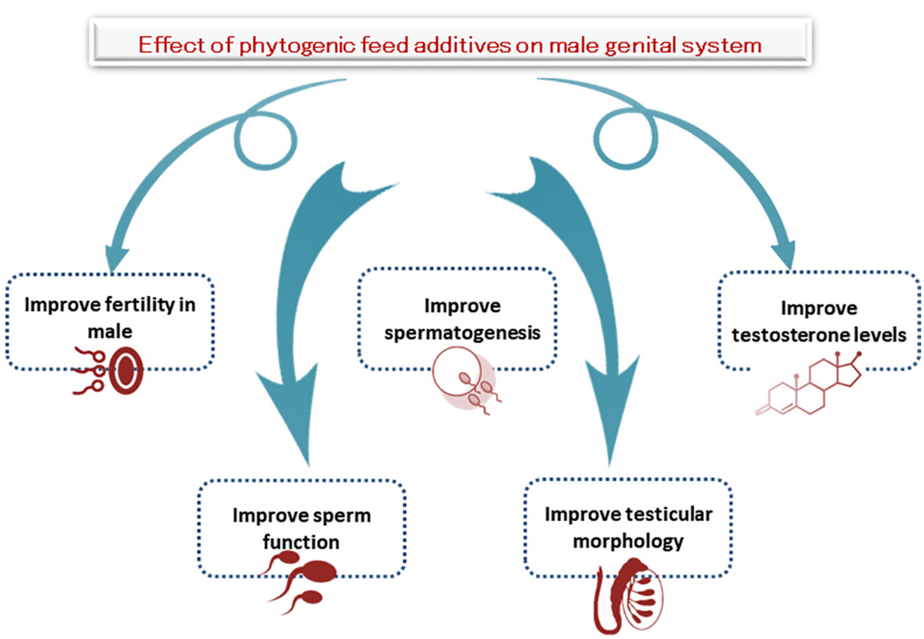

Fig. 1. Effects of phytogenic feed additives on male reproductive functions.

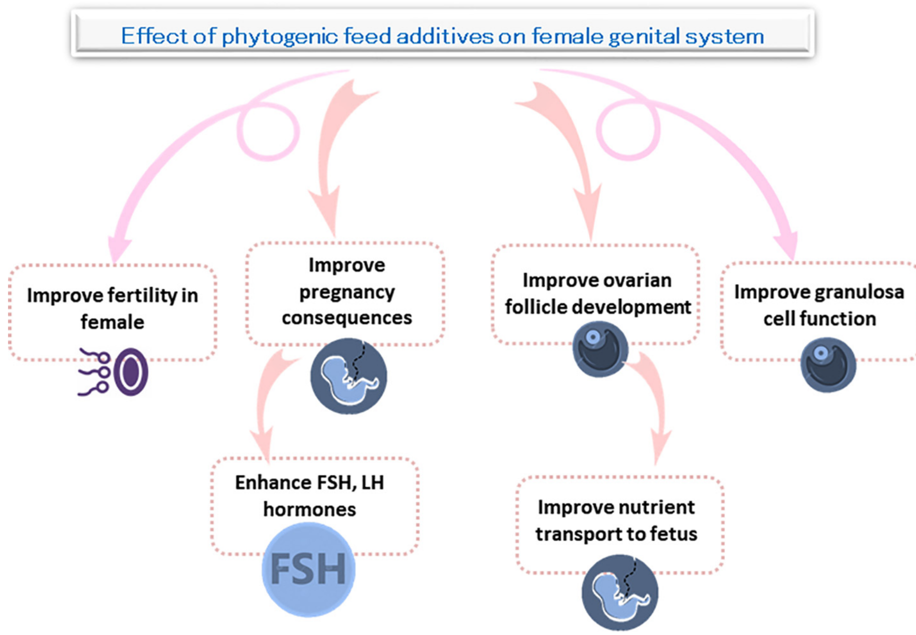

Fig. 2. Effects of phytogenic feed additives on female reproductive functions. Follicle-stimulating hormone (FSH); luteinizing hormone (LH).

respectively, compared with 20% for the control treatment (Nikhade et al., 2019).

The effects of phytogenic feed additives on female reproduction are illustrated in Fig. 2.

5. Phytogenic feed additives and assisted reproductive technology (ART)

A substantial amount of evidence shows that phytogenics have been used as antioxidants in ART. Several studies have indicated that the addition of herbal extracts to freezing extender positively affect semen quality after cryopreservation (Merati & Farshad, 2020). In addition, Merati & Farshad (2020) also reported that the addition of 10 mg/l ginger, enriched with 10 or 20 mg/l *Echinacea* extract, significantly improved the sperm motility and velocity indices of spermatozoa. The same study revealed a reduction in lipid peroxidation and acrosomal damage. Inclusion of ginger and/or *Echinacea* extract in ram semen extender improved the mitochondrial activity and normal sperm chromatin structure. The use of *Echinacea* extract and ginger enhanced the semen function and fertility of frozen-thawed ram spermatozoa owing to their antioxidant properties (Merati & Farshad, 2020).

Moradi et al. (2013) demonstrated that low doses (0.5% and 1%) of royal jelly (RJ) supplementation increased plasma membrane functionality and sperm kinetics during the freezing protocol in rams. Furthermore, the protective effect of RJ could be attributed to its antinitrosative and antioxidative abilities, and its antioxidant properties could be attributed to the phenolic content of its roots which share in reducing the lipid peroxidation and free radical scavenging assay (Sloley et al., 2001).

Mehdipour et al. (2017) showed that the inclusion of *Camellia sinensis* extract at doses of 5, 10, and 15 mg/l significantly enhanced the total antioxidant capacity, plasma membrane integrity, motility, and mitochondrial activity and significantly lowered the apoptotic spermatozoa and malondialdehyde (MDA) levels. Recently, Azimi et al. (2020) assessed the effects of purslane extract at concentrations of 25, 50, and 100 µg/ml on the quality of frozen-thawed goat spermatozoa. They found higher ($P < 0.05$) percentages of total motility, viability, integrity of the plasma membrane, and mitochondrial activity of sperm and lower proportions of dead and apoptotic spermatozoa and MDA levels for treatments with 50 µg of purslane extract/ml than for those with the control.

In another interesting study, Shokry et al. (2020) demonstrated that rams that received *M. oleifera* leaves extract (40 mg/kg body weight) reduced MDA levels in seminal plasma, DNA fragmentation, and acrosomal defects of sperm in cryopreserved semen. Additionally, Ahmed et al. (2020) revealed that tris citric acid extender supplemented with 1.0% green tea extract enhanced semen quality parameters, antioxidant enzymes, total antioxidant capacity, lipid peroxidation, and DNA fragmentation in buffalo bull spermatozoa, which increased semen longevity compared with the control during 45 and 90 min of incubation at 37 °C during IVF (Ahmed et al., 2020). Interestingly, the positive effects of phytogenic supplementation on freeze-thawing semen can significantly improve fertility *in vivo*. As mentioned above, Ahmed et al. (2019) found that adding 150 and 200 mM of quercetin to freezing medium enhanced buffalo semen quality and *in vivo* fertility indices after thawing.

In terms of assisted reproductive techniques for females, Barakat et al. (2015) reported that the addition of *M. oleifera* extract to oocyte maturation medium improved the oocyte maturation rate in sheep. This beneficial action of *M. oleifera* extract could be used to enhance the synthesis of essential proteins, e.g., maturation promoting factor, for oocyte maturation processes (Barakat et al., 2015). Additionally, this improvement could be related to the effect of *M. oleifera* extract in increasing calcium ions and modulating the expression of fertility-related genes in sheep oocytes (Barakat et al., 2015). Barakat et al. (2014) also concluded that green tea extract at 0.3 mg/ml in *in vitro* maturation medium significantly enhanced oocyte maturation and embryo development in sheep.

6. Phytogenic feed additives and anti-heat stress properties

The dominant climatic factors affecting livestock production include relative humidity, ambient temperature, solar radiation, wind speed, and atmospheric pressure. Among these issues, heat

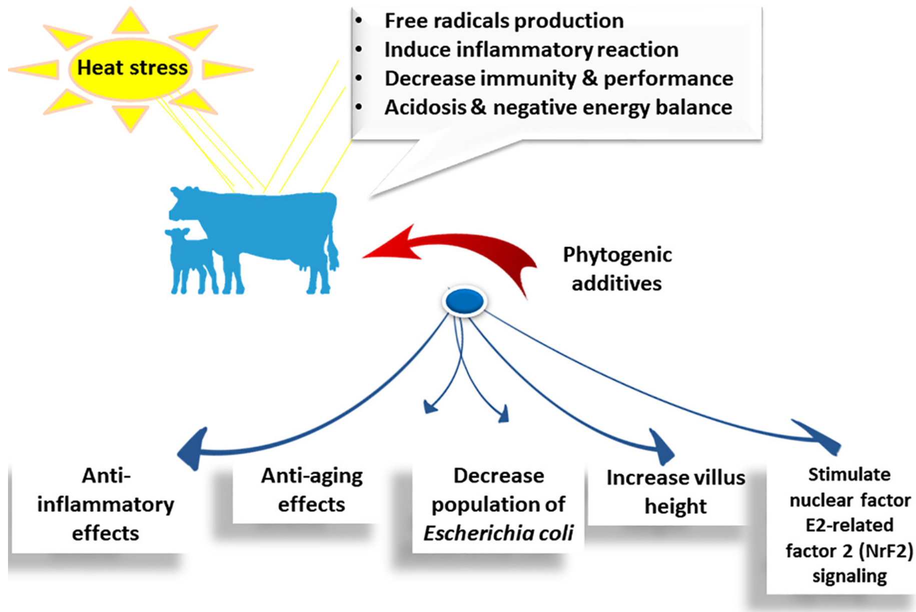

Fig. 3. Effects of phytogenic feed additives on heat stressed animals.

stress is the critical disruptor, particularly under recent climatic change. Heat stress has negative effects on the reproductive performance of all farm animals.

Observations in dairy cattle and buffaloes have shown an increasing trend in the occurrence of silent heat, corpus luteum dysfunction, repeated insemination, and embryonic loss, leading to reproductive failure after exposure to heat stress (Sigdel et al., 2020). Heat stress also affects the reproductive performance of males because it can decrease libido, semen quality, and testes function (El-Desoky et al., 2017; Wafa et al., 2017).

Dietary intervention, such as inclusion of phytogenic feed additives in diets, provide a putative approach that has been established to mitigate the negative influences of thermal stress in livestock (Wafa et al., 2017; Abdelnour et al., 2019; Abd El-Hack et al., 2020). Phytogenic feed additives have been given substantial attention because of their affordability, availability, safety, and potential antioxidant properties against heat stress. In this respect, 50 mg of *M. oleifera* extract/kg of body weight could enhance heat tolerance, semen quality, immunity, and health status of rabbit bucks reared under hot summer conditions (El-Desoky et al., 2017). Furthermore, *M. oleifera* (240 g/day/bull) was used to enhance the semen quality of buffalo bulls under unfavorable heat stress conditions (Wafa et al., 2017).

The effects of phytogenic feed additives on heat-stressed animals are illustrated in Fig. 3.

7. Negative impacts of phytogenic feed additives

It is vital to mention that phytogenic compounds can also have hazardous effects on reproductive traits, and some of them possess hormone-like effects (Hashem et al., 2018a, Hashem et al., 2018b; AboElsoud et al., 2019). In farm animals, specifically ruminants, the consumption of phytoestrogen-rich diets disturbs the hormonal balance in the animal body, leading to silent heat, progesterone deficiency, embryonic loss, and low semen quality (Hashem & Soltan, 2016).

In heifers, isoflavones in Berseem clover (*Trifolium alexandrinum*, phytoestrogen-rich roughage) disturb the hormonal balance by increasing the estrogen-to-progesterone ratio during early pregnancy, reducing the fertility of heifers. In seasonal anestrus ewes, feeding Berseem clover throughout seasonal anoestrus disrupts behavioral estrus by shortening the estrus duration, decreasing progesterone concentrations, increasing silent heat, and decreasing conception rates following estrus synchronization and subsequent fecundity (Hashem et al., 2018b).

In monogastric farm animals, such as rabbits, AboElsoud et al. (2019) found that oral administration of 20 mg of soybean isoflavones/kg body weight to adult rabbit bucks significantly improved their antioxidant status, whereas, treatment with either 5 or 20 mg of soybean isoflavones/kg body weight induced a hormonal discrepancy, resulting in decreased testes function. These findings highlight the sensitivity of the adult male reproductive system to activities of soybean isoflavones.

Further, Hashem et al. (2018a) found that prolonged consumption of dietary lignans (linseed-based diet) or isoflavones (soybean-based diet) by adult male rabbits did not influence sperm serializability. The beneficial action of phytoestrogen could be attributed to the phenolic compound, which has potent antioxidant properties; however, phytoestrogens induced noticeable reductions in sexual activity and steroidogenesis accompanied by an alteration in semen quality variables (Hashem et al., 2018a).

Another adverse effect of phytogenic compounds is indicated by Sirotkin et al. (2019). They found that granulosa cells in cattles treated with quercetin showed reduced proliferation and apoptosis and decreased *P*4 and E2 release (Sirotkin et al., 2019). The hypocholesterolemic impact of yucca might be associated with a reduction in substrate for the production of steroid hormones, resulting in the suppression of *P*4 release by the ovaries (Khalifa et al., 2014).

The pro-apoptotic effect of yucca extract was also detected after 1 month of feed supplementation in ewes, whose granulosa cells contained a high proportion of bax antigens. However, no effect was found for the proliferation of granulosa cells (Vlčková et al., 2017). Few articles on the effects of phytogenics on reproductive organ morphology are available.

Vlčková et al. (2017) reported that ewes fed with yucca powder for 1 month showed reduced ovarian folliculogenesis in the early antral follicle stage through reduction in the size of these follicles; however, the yucca powder had no significant effect on the size or number of larger follicles and therefore, the size or weight of the ovaries.

8. Conclusion

This review identified a relatively large number of phytogenic feed additives having beneficial effects on sexual behavior, hormone profiles, and sperm quality in both fresh and preserved semen. Moreover, the results indicated that these additives provide promising options for enhancing the reproductive efficiency of females in terms of *in vitro* fertility and conception rates. Although beneficial effects of phytogenics have been found, including antioxidant, anti-inflammatory, and immunostimulatory properties, future studies should address the different effects of phytogenics on males and females in reproductive processes.

Author contributions

All authors were equally contributed in writing this review article.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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