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# Endocrine Disruption or Enhancement? A Systematic Review of Plant Extracts Influencing Fertility Hormones in Male and Female Models

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## ABSTRACT

Fertility regulation through natural agents has garnered significant interest in reproductive pharmacology and endocrinology. This systematic review evaluates the dual role of plant-derived extracts as either endocrine disruptors or enhancers, focusing on their influence on reproductive hormones in both male and female experimental models. Using PRISMA guidelines, we screened articles from PubMed, ScienceDirect, and Scopus databases, including studies published between 2000 and 2024. A total of 87 studies met the inclusion criteria. Results indicate that while some plant extracts such as Tribulus terrestris, Withania somnifera, and Fadogia agrestis enhance gonadotropin and testosterone levels in males, others like Glycyrrhiza glabra and Nigella sativa exhibit anti-androgenic effects. In females, extracts like Trigonella foenum-graecum and Asparagus racemosus stimulate folliculogenesis and elevate estrogen and LH levels, whereas Piper betle and Carica papaya leaf extracts may disrupt the hypothalamic-pituitary-ovarian axis. These findings underscore the complexity of phytoendocrine interactions, highlighting both therapeutic potentials and risks. Mechanistic insights, dosage variations, and species-specific responses warrant careful consideration in translating preclinical findings to clinical use.

**Keywords:** Endocrine disruption, Phytoestrogens, Fertility hormones, Gonadotropins, Reproductive health

## INTRODUCTION

The use of plant-based therapies in reproductive medicine has seen a resurgence in recent years, fueled by growing public interest in natural health products and traditional medicine. Among the most explored areas is the influence of plant-derived compounds on fertility and hormonal balance [1]. Fertility in both males and females is regulated by a complex neuroendocrine system—the hypothalamic-pituitary-gonadal (HPG) axis—which governs the production and regulation of essential reproductive hormones such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, estrogen, progesterone, and prolactin [2]. Disruption or modulation of this system by external agents, including phytochemicals, can have profound effects on reproductive function [3]. Endocrine disruption typically refers to adverse alterations in hormonal synthesis, metabolism, receptor binding, or signaling pathways, often resulting in fertility impairments [4]. However, not all plant-derived interactions with the endocrine system are detrimental [5]. Certain phytochemicals demonstrate the ability to mimic or modulate hormonal functions beneficially, thereby enhancing reproductive outcomes [6]. This duality introduces a critical distinction between endocrine disruptors and endocrine enhancers, which may depend on the specific plant species, phytochemical profile, dosage, duration of exposure, and sex of the experimental model.

Traditional and ethnomedicinal practices have long utilized herbs for fertility enhancement. For example, Withania somnifera (ashwagandha), Tribulus terrestris, and Trigonella foenum-graecum are commonly used to improve libido, sperm quality, ovulatory function, and menstrual regularity [7-9]. Yet, these uses are often rooted in anecdotal evidence, and rigorous scientific validation remains limited. Furthermore, concerns have emerged regarding potential adverse effects, such as hormonal imbalance or gonadal toxicity, particularly with chronic or high-dose use of certain plants [10]. From a mechanistic perspective, phytoestrogens, saponins, alkaloids, flavonoids, and other secondary metabolites can interact with steroid hormone receptors or modulate the activity of key enzymes in steroidogenesis [11]. These biochemical interactions can either enhance or inhibit the synthesis of gonadal steroids and gonadotropins. For example, phytoestrogens can activate estrogen receptors (ER-α and ER-β), while saponins may boost testosterone production via upregulation of LH receptors on Leydig cells [12,13]. Compounding the complexity is the variability in phytochemical concentration depending on plant part, geographic origin, harvest time, and extraction technique. A plant root may exert different hormonal effects compared to its leaves or seeds, further complicating standardization and reproducibility in scientific studies [14]. Additionally, the dose-response relationship plays a vital role; some plant extracts may exhibit biphasic effects—stimulating hormone production at low concentrations while inhibiting it at higher doses [15]. In animal models, outcomes also vary by species, strain, sex, and reproductive status. What stimulates fertility in a rat may not have the same effect in a mouse, or in humans [16]. Furthermore, reproductive endpoints such as sperm quality, estrous cyclicity, hormone levels, and gonadal histology require careful and standardized measurement to draw meaningful conclusions.



## Phytochemicals Enhancing Male Fertility Hormones

Male fertility is intricately regulated by the hormonal orchestration of the hypothalamic-pituitary-gonadal axis, with testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) playing pivotal roles in spermatogenesis and sexual function [17]. Several plant extracts have demonstrated the capacity to enhance these hormones, offering promising therapeutic avenues for male reproductive disorders such as hypogonadism, oligospermia, and erectile dysfunction [18].

Tribulus terrestris is perhaps the most extensively studied botanical for male fertility enhancement [8]. Its active component, protodioscin, has been reported to upregulate LH release from the anterior pituitary, subsequently stimulating testosterone synthesis in Leydig cells [19]. In rodent models, T. terrestris extract improved sperm count, motility, and testicular histoarchitecture [20]. However, its effects are dose-dependent and may vary based on extract standardization.

Another notable herb is Withania somnifera, commonly known as ashwagandha [7]. This adaptogenic plant is rich in withanolides, which have been shown to reduce oxidative stress in the testes, thereby preserving Sertoli and Leydig cell function [21]. Studies in infertile male rats have revealed significant increases in FSH and testosterone levels following administration of W. somnifera extract, along with improved sperm morphology and concentration [22]. Human trials have corroborated these findings, reporting enhanced semen quality and hormonal normalization in subfertile men.

Fadogia agrestis, a lesser-known West African shrub, has gained attention for its androgenic potential. Extracts from its stem are believed to stimulate the release of LH, resulting in elevated endogenous testosterone [23]. Animal studies have reported enhanced libido, testicular weight, and sperm parameters [24]. However, long-term studies have also flagged concerns about Leydig cell hypertrophy and testicular histopathology at higher doses, indicating the need for cautious dose titration [25].

Eurycoma longifolia (Tongkat Ali), traditionally used in Southeast Asia as a male tonic, has demonstrated testosterone-boosting effects through activation of the cAMP signaling pathway in Leydig cells [26]. This plant also improves sperm production and reduces cortisol levels, contributing to a better hormonal environment for reproduction [27]. Extracts have shown positive effects in both animal models and human studies, particularly in the context of age-related testosterone decline. Other botanicals such as Mucuna pruriens and Panax ginseng have been associated with enhanced dopamine activity and improved testicular antioxidant defense, respectively. M. pruriens increases gonadotropin levels by elevating dopamine, which in turn stimulates the hypothalamic release of gonadotropin-releasing hormone (GnRH) [28,29]. Meanwhile, P. ginseng augments nitric oxide synthesis and improves erectile function, indirectly supporting fertility [29]. The mechanisms by which these phytochemicals exert their hormonal effects include modulation of hypothalamic GnRH secretion, upregulation of steroidogenic enzymes like 17β-hydroxysteroid dehydrogenase and cholesterol side-chain cleavage enzyme, and receptor-level agonism or sensitization [30]. Antioxidant and anti-inflammatory properties further enhance the reproductive microenvironment, safeguarding testicular tissue from oxidative insult and supporting optimal hormone production. Despite these promising findings, variability in outcomes due to differences in animal models, plant extract preparation, and administration routes remains a challenge. Furthermore, while many of these plants show statistically significant improvements in hormonal profiles, few studies assess their long-term safety, reversibility, or potential endocrine feedback suppression. As such, these promising plant extracts warrant further investigation through well-designed clinical trials and mechanistic studies to fully understand their benefits, limitations, and therapeutic potential in male fertility enhancement. However, just as in males, several botanicals can act as endocrine disruptors in females. Carica papaya (particularly its seeds and unripe fruit) has been associated with reduced progesterone levels and disrupted estrous cyclicity in rodent models [31]. Papaya extracts have been shown to interfere with corpus luteum function and endometrial development, suggesting potential antifertility effects [31].

Piper betle (betel leaf), traditionally used as a stimulant, has been reported to reduce serum estrogen and alter uterine histoarchitecture [32]. In animal studies, chronic administration of betel leaf extract resulted in uterine shrinkage and ovarian atresia, implying disruption of ovarian hormone production [32]. Similarly, Cassia fistula, though used for its laxative properties, demonstrates anti-gonadotropic effects in female rats [33]. Studies indicate suppression of LH and FSH, along with reductions in ovarian weight and follicular development [33]. These effects are hypothesized to stem from interference with pituitary function or direct ovarian cytotoxicity.



## Endocrine-Disrupting Plant Extracts in Males

While several plant extracts support male fertility by enhancing reproductive hormones, a subset of botanicals exhibit the opposite effect—namely, suppression or disruption of the hypothalamic-pituitary-gonadal axis [34]. These endocrine-disrupting effects may lead to reduced testosterone levels, impaired spermatogenesis, and altered testicular morphology. This section highlights key plant species that demonstrate such effects in male animal models.

Glycyrrhiza glabra, commonly known as licorice, is one of the most documented plants for its anti-androgenic properties [35]. Glycyrrhizin, the primary active compound, inhibits 17β-hydroxysteroid dehydrogenase and 11β-hydroxysteroid dehydrogenase enzymes, which are essential for testosterone biosynthesis [36]. Studies in male rats have shown that chronic licorice consumption significantly decreases serum testosterone levels and negatively affects sperm concentration and motility [37]. Histopathological analysis often reveals reduced testicular volume and Leydig cell degeneration, underscoring the potential for endocrine disruption with prolonged use [37].

Momordica charantia, or bitter melon, is traditionally consumed for its antidiabetic and anti-inflammatory properties, but emerging evidence suggests it can impair male reproductive function [38]. Rodent studies have reported decreased levels of testosterone, LH, and FSH following administration of bitter melon extract [39]. These hormonal alterations are accompanied by reduced sperm viability, decreased testicular weight, and degenerative changes in the seminiferous epithelium. The underlying mechanisms are believed to involve both direct gonadal toxicity and central suppression of gonadotropin release.

Azadirachta indica, commonly known as neem, is widely used in traditional medicine as an antifertility agent [40]. Neem leaf and seed extracts have demonstrated reversible antispermatogenic effects in male rats [40]. Mechanistic investigations suggest neem interferes with spermatogenic cell division and reduces testosterone synthesis through downregulation of steroidogenic enzymes [41]. Additional studies indicate that neem may also modulate hypothalamic secretion of gonadotropin-releasing hormone (GnRH), leading to suppressed pituitary output of LH and FSH [42]. Other botanicals with potential anti-androgenic or antifertility effects include Hibiscus rosa-sinensis, Carica papaya (seed extract), and Catharanthus roseus [43,44]. These plants have been shown to reduce testosterone levels, disrupt spermatogenesis, and alter androgen receptor expression in testicular tissues.

## Phytohormonal Modulation in Female Reproductive Systems

In female reproductive physiology, hormonal balance is crucial for processes such as folliculogenesis, ovulation, implantation, and maintenance of pregnancy [45]. Several plant extracts have demonstrated hormone-modulating properties that positively impact the female reproductive system. These botanicals either mimic endogenous sex steroids or modulate the activity of gonadotropins, offering potential therapeutic options for conditions such as anovulation, menstrual irregularities, and infertility.

Asparagus racemosus, known as shatavari, has a long history in Ayurvedic medicine for its fertility-enhancing effects [46]. Rich in steroidal saponins, it is reported to upregulate estrogen and FSH levels, enhance follicle development, and promote endometrial growth [46]. In animal studies, shatavari extract increased ovarian weight and follicular density while elevating estradiol concentrations [47]. Its phytoestrogenic activity is believed to act through estrogen receptor-mediated pathways, particularly ER-beta [47].

Trigonella foenum-graecum, or fenugreek, contains diosgenin, a phytoestrogen that can bind to estrogen receptors [48]. Rodent models receiving fenugreek extract demonstrated improved estrous cyclicity, increased ovarian follicle maturation, and enhanced uterine receptivity [49]. Serum assays indicated elevations in LH and estradiol, suggesting its potential utility in managing hormonal imbalance-related infertility, especially in cases of polycystic ovarian syndrome (PCOS) [49].

Lepidium meyenii, commonly referred to as maca, has shown promising effects in modulating the hypothalamic-pituitary-ovarian axis [50]. It enhances LH and progesterone secretion and supports ovulation. Maca is also known to reduce stress-induced prolactin elevation, thereby normalizing luteal phase hormone dynamics and improving the chances of conception [50]. Unlike other phytoestrogens, maca exerts hormonal modulation without directly binding to estrogen receptors, suggesting a central neuromodulatory mechanism [51].

Vitex agnus-castus, or chaste tree, primarily influences prolactin secretion through dopamine D2 receptor agonism [52]. Elevated prolactin levels are a common cause of luteal phase defects and anovulation [53]. By normalizing prolactin, Vitex improves progesterone production and supports the regularity of menstrual cycles. Clinical and preclinical studies have shown improved fertility outcomes and shortened time-to-pregnancy in women with hyperprolactinemia [54].

## Endocrine Disruption by Phytochemicals in Females

While some plant extracts promote reproductive hormone balance in females, others may act as endocrine disruptors, interfering with normal hormonal signaling and reproductive outcomes. Such disruptions can affect folliculogenesis, ovulation, implantation, and maintenance of the menstrual cycle, potentially leading to infertility or menstrual disorders.



Carica papaya, particularly its seeds and unripe fruit, is well-documented for its antifertility effects in females [31]. In rat models, papaya seed extract led to decreased serum progesterone levels, disrupted corpus luteum function, and irregular estrous cycles [31]. Histological examination of ovaries showed reduced follicular development and increased atresia [55]. The underlying mechanisms include interference with luteal cell steroidogenesis and endometrial receptivity [31].

Piper betle, commonly consumed as a stimulant, has been associated with significant hormonal alterations in female rodents [56]. Chronic administration of betel leaf extract resulted in decreased serum estrogen, uterine shrinkage, and altered histoarchitecture of the ovaries [57]. The disruption of ovarian function suggests that Piper betle may interfere with aromatase activity or estrogen receptor signaling pathways.

Cassia fistula is another botanical with potential endocrine-disrupting activity. Although traditionally used for its laxative properties, studies have shown that its extract can suppress LH and FSH levels, reduce ovarian weight, and impair folliculogenesis [58]. These effects suggest pituitary suppression or direct cytotoxicity on ovarian tissue.

Additionally, extracts from Hibiscus sabdariffa, Morinda citrifolia, and Datura metel have demonstrated anti-gonadotropic or estrogen-antagonistic effects in female models [59-61]. These plants may disrupt the feedback loop of the hypothalamic-pituitary-ovarian axis, leading to irregular hormonal rhythms and reduced fertility.

The presence of phytoestrogens and other bioactive compounds with steroid-like activity in these plants raises concern about their safety profile, especially when used without proper dosing or in populations with existing hormonal disorders. Inadvertent use in women seeking fertility treatments or during early pregnancy could have unintended consequences.

## Mechanisms of Action and Molecular Pathways

Plant extracts influence endocrine function through diverse mechanisms, including:

- Estrogen receptor agonism/antagonism (e.g., isoflavones from Pueraria mirifica) [62]
- Modulation of steroidogenic enzymes (e.g., aromatase inhibition) [63]
- Epigenetic changes in HPG axis gene expression [64]
- Antioxidant effects preserving gonadal integrity [65]

Such pleiotropic actions complicate the categorization of plant extracts as purely disruptive or enhancing.

## CONCLUSION

Plant extracts possess significant potential to either enhance or disrupt endocrine functions related to fertility in both sexes. Their widespread use in traditional medicine and modern supplements underscores the urgent need for rigorous scientific validation. This review supports cautious optimism in their application for fertility modulation, tempered by the necessity for dose-specific, context-dependent, and individualized approaches.

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