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Review

A Review on Male Infertility and Herbal Medicine: Complementary and Alternative Therapies in Animal Models

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Abstract

Various factors contributing to male infertility include genetic determinants, hormonal/neurological imbalance, erectile/libido disorders, genital tract injuries, and toxic/ischemic testicular injuries. Herbs increase sperm count and quality parameters, as well as sexual performance in infertile men, through various mechanisms. For this purpose, efforts were made to investigate effective plants in treating infertility, focusing on those studied in animal research. In this review, we explored the latest findings from animal studies on the therapeutic applications of medicinal plants in male infertility. Based on MeSH keywords, 250 animal studies investigating the effects of herbs on male infertility were reviewed, 72 of which were selected after removing duplicated and unrelated articles. The search was conducted in the Scientific Information Database, the World Health Organization database, Web of Science, Science Direct, Iranmedex, Cochran Library, PubMed, and Google Scholar. The mechanisms underlying the therapeutic effects of herbs on male infertility caused by hormonal disorders, oxidative stress, cytokines, inflammatory pathways, as well as erectile and libido disorders were discussed. Aphrodisiac, spermatogenesis-inducing compounds, antioxidants, anti-inflammatory agents, and androgenic compounds, including anthocyanins, proanthocyanidins, ginsenosides, protodioscin, quassinoids, sesquiterpenes, diosgenin, phyto-oestrogens, thymoquinone, and bajijiasu, in these plants increase male fertility by affecting the hypothalamic-pituitary-gonadal axis and improving sperm's functional parameters and fertility indices in relation with seminiferous tubules.

Keywords

Male; infertility; medicinal plants; libido; spermatogenesis

1. Introduction

Infertility is defined as a couple's inability to conceive a child after one year or more of regular unprotected sexual intercourse. Over 15% of couples suffer from infertility, approximately 50% of whom receive assistance for male infertility [1, 2]. Unhealthy lifestyle practices (such as inappropriate diets, smoking, and alcohol abuse), varicocele, hormonal imbalances, traumatic injuries/infections of the urogenital tract, genetic disorders, occupational hazards (such as inhalation of toxic compounds like lead, cadmium, and mercury), along with the use of androgenic anabolic steroid derivatives, exert deleterious effects on testosterone production and semen quality, consequently resulting in male infertility [3, 4].

Diverse factors, such as the suppression of the hypothalamic-pituitary-gonadal axis (HPGA), excessive production of reactive oxygen species (ROS), inadequate nutrition, inflammatory processes (resulting in the secretion of pro-inflammatory cytokines), and enhancement of apoptotic pathways, have been documented to reduce or suppress male fertility, ultimately leading to a decrease in the fertility rate [5]. Currently, 1,500-2,000 genes have been noted to be involved in spermatogenesis, and any interference with the expression of these proteins can lead to oligo-terato-spermia disorders [6].

Herbs originate from plants and plant extracts from various natural resources, including plant leaves, bark, flowers, roots, fruits, and berries. Evidence-based herbal medicine may present an effective treatment for male and female infertility [7-9]. However, 25% of men have permanent infertility, which is irreversible and incurable for various reasons, such as germ cell arrest, germ cell aplasia (persistent azoospermia), and severe hypo-spermatogenesis [10]. Herbs containing compounds such as polyphenols and aphrodisiac agents can improve testosterone levels, sexual performance, sperm quality (e.g., count, motility, viability), and libido. In most developing countries, combinational therapy (including surgery, experimental methods, and medicinal plants) is generally used to treat infertility and achieve the best results. For this purpose, in the present study, medicinal plants used in animal research were reviewed for use in human studies (clinical trials). Plants that can potentially serve as pharmaceutical adjuncts or complementary drugs to enhance libido, reinforce the Hypothalamic-Pituitary-Gonadal Axis (HPGA), and exhibit anti-inflammatory-antioxidant effects to improve male fertility were investigated.

2. Materials and Methods

2.1 Search Strategy and Study Framework

Based on the checklist for conducting systematic reviews (i.e., PRISMA guidelines) and the results of our initial literature search, 250 papers published from 1999 to 2023 and obtained from Wiley Online Library, PubMed, Scientific Information Database, World Health Organization database, Iranmedex, Cochran library, and Google Scholar were reviewed. In this study, the literature search was conducted using MeSH keywords, including "male infertility," "herbal medicine and male infertility," "herbal medicine and HPGA," "antioxidant effects," "anti-inflammatory effects," "aphrodisiac effects," and "libido stimulating effects." In addition, the scientific names of traditional medicinal plants were used. This review aims to discuss the results of studies on animal models exploring the antioxidant and anti-inflammatory effects of medicinal plants and their effects on HPGA and male sexual function.

2.2 Inclusion Criteria

English-language articles evaluating the effects of medicinal plants on male infertility and their different mechanisms were selected. Overall, 58 studies conducted on animal models investigating the positive effects of different plants on the male reproductive system were selected. Fifteen studies that evaluated the botanical characteristics, general biological interactions, and the effects of plants on *in vitro* models were selected for inclusion.

2.3 Exclusion Criteria

Non-English language papers, those with insufficient data, studies with poor methodology, those assessing indirect effects of herbs, and studies reporting ineffective (negative) effects on male fertility were excluded from the analysis.

3. Results

From 1999 to 2023, a total of 250 eligible papers were identified. After reviewing their titles and abstracts, 145 duplicates and 73 irrelevant studies were excluded. After eliminating duplicate and unrelated studies, 72 articles investigating the benefits or limitations of different herbs on male infertility in different *in vitro* and *in vivo* (animal) models were scrutinized (Figure 1).

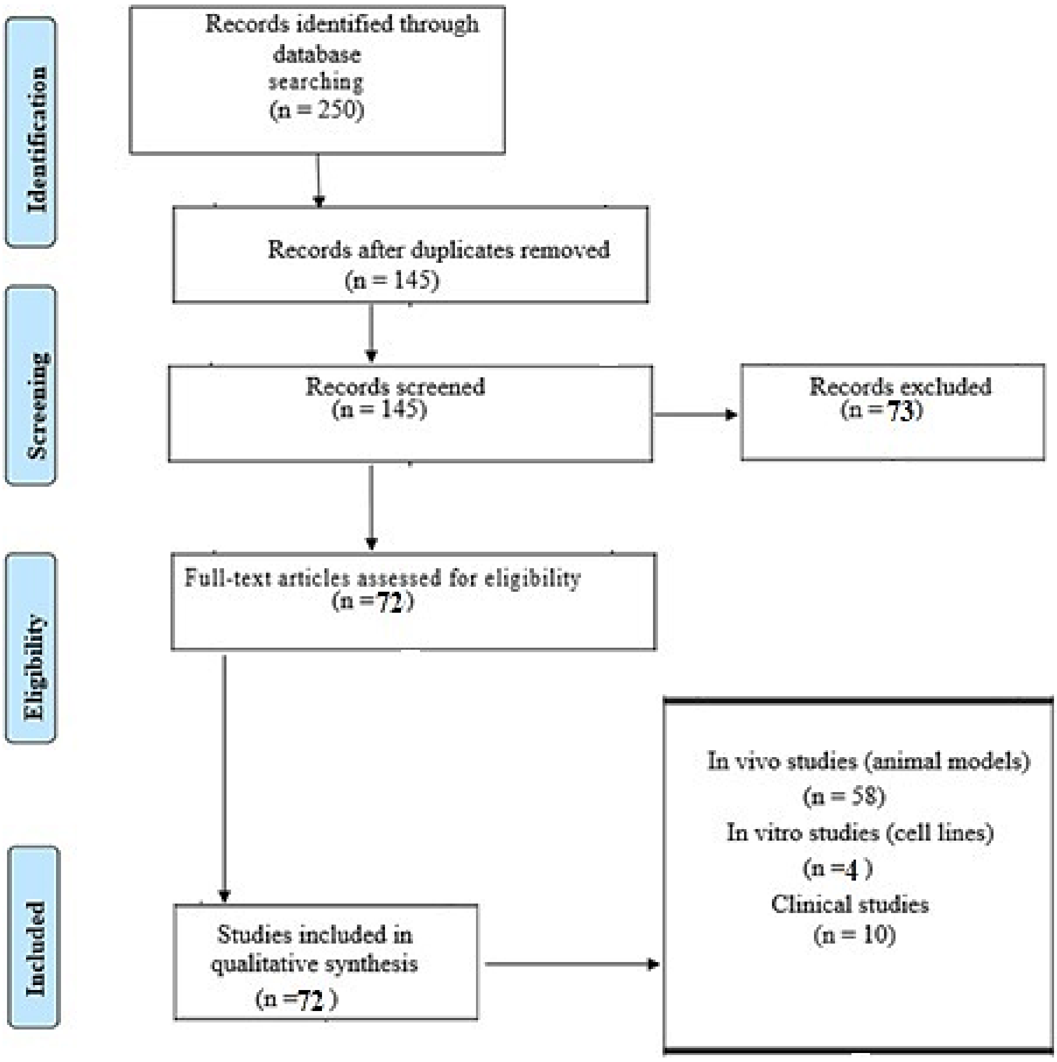

Figure 1 Flowchart of the study, including literature search, quality assessment, exclusion by reasons, and the final inclusion of studies.

After reviewing non-duplicated and related articles, the effects of Morinda officinalis L., *Annona muricat*a L., *Ginkgo biloba* L., *Kaempferia parviflora* L., *Apium graveolens* L., *Tinospora cordifolia* L., *Epimedium brevicornum* L., *Zingiber officinale* L., *Terminala catappa* L., *Syzygium aromaticum* L., *Cynomorium coccineum* L., *Pfaffia paniculata* L., *Chlorophytum borivilianum* L., *Butea superba* L., *Anthocleista djalonensis* L., *Nasturtium officinale* L., *Vaccinium arctostaphylos* L., *Fadogia agrestis* L., and *Ruta chalepensis* L. was investigated on infertility in different animal model (Table 1).

Table 1 Medicinal plants showing effectiveness in treating male infertility.

References	Plant	Dosage used/duration	Plant part	Animal model	Route of administration	Observed effects
[11]	*Morinda officinalis* L.	160 mg/kg/30 days	Leaf	Mice	Gavage	Increase in serum testosterone levels and improvement of sperm functional parameters ($p < 0.05$)
[12]	*Annona muricata* L.	5 and 10 ml/kg/65 days	Fruit	Rat	Gavage	Improvement of sperm functional parameters ($p < 0.05$)
[13]	*Ginkgo biloba* L.	50 mg/kg/40 days	All parts of the plant	Rat	Gavage	Improvement of antioxidant indices (increased SOD levels and decreased MDA levels) ($p < 0.05$) Improving the level of T ($p < 0.05$) Improvement of apoptosis and inflammatory indicators (reduction of IL-1β, TNF-α, Bax, NF-κB, p53, and caspase-3) ($p < 0.05$)
[14]	*Kaempferia parviflora* L.	20 and 40 mg/kg for 5 weeks	All parts of the plant	Rat	Gavage	Increased sexual potency, aphrodisiac effects, antioxidant effects, increased testicular blood flow, and improved sperm functional parameters ($p < 0.01$)
[15]	*Apium graveolens* L.	100 and 200 mg/kg/30 days	Leaf	Rat	Gavage	Improved sperm functional parameters, increase in spermatogenic lineage differentiation, and improvement of testicular histomorphometric parameters ($p < 0.05$)
[16]	*Tinospora cordifolia* L.	1 g/kg/6 months	All parts of the plant	Rams	Gavage	Improvement of sperm functional parameters and testicular histomorphometric indices ($p < 0.01$)

[17]	*Epimedium brevicornum* L.	100-1000 µg/0.1 ml solvent/2 hr after oral administration	Leaf	Rat	Gavage	Increased libido, sexual potency, and erection ($p < 0.001$)
[18]	*Zingiber officinale* L.	50-150 mg/kg/48 days	Root	Rat	Intraperitoneal injection	Strengthening of the HPG axis (increased serum testosterone levels), improvement of sperm functional parameters and testicular histomorphometric indices ($p < 0.05$)
[19]	*Terminala catappa* L.	1.5 g/kg/7 days	Seed	Rat	Intraperitoneal injection	Increased libido, sexual vigor, sexual potency, ejaculation latency, and erection ($p < 0.001$)
[20]	*Syzygium aromaticum* L.	500 mg/kg/7 days	Flowers	Rat	Intraperitoneal injection	Increased libido, mating, and intromission frequencies, sexual potency, ejaculation latency, and erection ($p < 0.001$)
[21]	*Cynomorium coccineum* L.	47 mg/100 mg daily diet/14 days	All parts of the plant	Rat	Intraperitoneal injection	Improvement of sperm functional parameters and testicular histomorphometric indices ($p < 0.001$)
[22]	*Pfaffia paniculata* L.	0.25-1 mg/kg/1 hr	Root	Rat	Intraperitoneal injection	Increased libido, mating and copulatory performance, inter-copulatory interval, sexual potency, ejaculation latency, and erection ($p < 0.05$)
[23]	*Chlorophytum borivilianum* L.	125 and 250 mg/kg/1-60 days	Root	Rat	Gavage	Increased libido, sexual vigor, sexual arousal, ejaculation latency, and sperm functional parameters ($p < 0.05$)
[24]	*Butea superba* L.	250 mg/kg/60 days	Root	Rat	Gavage	Improvement of sperm functional parameters and testicular histomorphometric indices ($p < 0.001$)
[25]	*Anthocleista djalonensis* L.	200 mg/kg/60 days	Root	Rat	Gavage	Strengthening of the HPG axis (increased serum testosterone levels) and improvement of sperm functional parameters ($p < 0.001$)

[2]	*Nasturtium officinale* L.	25-100 mg/kg/40 days	Leaf	Mice	Gavage	Strengthening of the HPG axis (increased serum testosterone, FSH, and LH levels), improvement of sperm functional parameters, and antioxidant effects ($p < 0.001$)
[5]	*Vaccinium arctostaphylos* L.	100-400 mg/kg/50 days	Fruit	Mice	Gavage	Strengthening of the HPG axis (increased serum testosterone, FSH, and LH levels), anti-apoptotic activity, improvement of sperm functional parameters, antioxidant effects ($p < 0.001$)
[26]	*Fadogia agrestis* L.	18-100 mg/kg/1-5 days	Stem	Rat	Intraperitoneal injection	Strengthening of the HPG axis (increased serum testosterone, FSH, and LH levels), increase in mount frequency intromission, ejaculation latency, and sperm functional parameters ($p < 0.001$)
[27]	*Ruta chalepensis* L.	0.5-2 g/kg/30 days	Leaf	Rat	Gavage	Strengthening of the HPG axis (increased serum testosterone, FSH, and LH levels), improvement of testicular histomorphometric indices and sperm functional parameters ($p < 0.05$)

HPG: Hypothalamic-pituitary-gonadal, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone.

4. Discussion

4.1 Interactions between Medicinal Plants and Male Reproductive System

Some herbs, such as *Rubus coreanus* L. (Raspberry) and *Eurycoma longifolia Jack* L. (Tongkat Ali), improve sperm's functional parameters by modulating gene expression and inducing the cyclic adenosine monophosphate-responsive element modulator protein, which drives the steroidogenesis cascade to increase testosterone synthesis in testis [28, 29]. Studies have shown that some compounds derived from herbs (e.g., *Tribulus terrestris* L, *Corchorus depressus* L, and Pedalium murex L), including protodioscin and proanthocyanidin-B1, increase the concentration of dihydrotestosterone by stimulating Sertoli cells and boosting the activity of 5α-reductase, increasing free testosterone, dihydrotestosterone, dehydroepiandrostenedione, and the height of the testicular germinal epithelium, which improve sperm quality parameters, libido, and sexual performance in men undergoing infertility treatment [30-32].

The leaf extract of *Mucuna pruriens* L. (velvet bean), due to its aphrodisiac compounds (β-sitosterol, prurienine, prurieninine, prurienidine, and saponins), increased the frequency of erections and intromission, quick/long flip, ejaculation latency, total reflex, and testosterone concentrations in animal models [33, 34]. Some plant-derived compounds (in *Pedalium murex* L. and *Corchorus depressus* L.), including diosgenin, are analogs of testosterone derivatives and convert testosterone and estrogen to dehydroepiandrosterone, ultimately improving the penile erection index, sperm quality parameters, sexual behavior, and fertility rate [31-34]. Bajijiasu, a compound derived from Morinda officinalis L., has been reported to have androgenic properties. In addition to its antioxidant properties, like protecting sperm's deoxyribonucleic acid against oxidative damage by ROS, this compound activates the mitogen-activated protein kinase phosphorylation and kisspeptin 1- G-protein-coupled receptor pathways. It also stimulates gonadotropin secretion and testosterone production, which ultimately improves sperm quality and induces the differentiation of the spermatogenic lineage during the normal cycle of spermatogenesis [35, 36].

Quassinoids in some medicinal plants (such as *Eurycoma longifolia* L.) present androgenic activity by concentrating testosterone as a prodrug in androgen-deficient idiopathic male sterility. Due to its androgenic role, this compound is used in men with late-onset hypogonadism and estrogen-induced infertility to improve sperm quality and sexual performance [37]. *Nigella sativa* L.-derived thymoquinone has been shown to enhance HPGA, which concentrates testosterone through this axis and affects the activity of Leydig and Sertoli cells [38]. Animal models and human studies show that this compound can increase the weight of the testis and epididymis and the serum levels of the luteinizing hormone, sperm count, and daily sperm production [39, 40].

The leaves of some plants, including Apium graveolens L., are full of phyto-estrogenic compounds that not only play a role in testosterone concentration but also increase the mRNA level of the CYP19 (aromatase cytochrome P450) enzyme, maintaining the natural cycle of spermatogenesis, increasing the differentiation of spermatogonia cells (both type A and B) to spermatids, and ultimately improving sperm functional parameters [41, 42]. Rose oil has been used in traditional medicine to increase libido and sexual competency. Its compounds can improve the natural cycle of spermatogenesis, concentrate testosterone, increase sperm count, and reduce abnormal sperm [28, 43, 44].

4.2 Medicinal Plants, Aphrodisiac Effects, and Males' Sexual Behavior

Research indicates that extracts from plants such as *Kaempferia parviflora* L. (20 and 40 mg/kg for 5 weeks) containing potent aphrodisiac compounds have the potential to enhance sexual performance by augmenting libido and ameliorating ejaculatory latency and erectile dysfunction [29, 30]. Another study showed that the extract of *Epimedium brevicornum* L. enhanced sexual performance in males, and dietary supplements containing 100-1000 µg/0.1 mL solvent of the plant extract, by increasing blood pressure in the cavernous system of the penis improved the time and frequency of penile erection in rats [31-33].

Usage of the extracts of Terminalia *catappa* L. (1.5 g/kg/7 days) and Syzygium *aromaticum* L. (500 mg/kg/7 days) for seven consecutive days was found to improve libido (ejaculation), sexual vigor (intromission frequency), sexual performance (prolongation of ejaculation latency), and premature ejaculation [34-37]. In the spermatogenesis cycle in rats spanning 65 days, *Annona muricata* L. extract (5 and 10 ml/kg/for 65 days) not only preserved testicular tissue structure with normal spermatogenesis cycles but also prevented sperm apoptosis, strengthened the HPGA axis, and increased testosterone concentration through its aphrodisiac effects [28]. Additional studies on plants such as *Pfaffia paniculata* L. (0.25-1 mg/kg/10 days) and *Chlorophytum borivilianum* L. (125 and 250 mg/kg/60 days) in rats demonstrated improved libido, sexual vigor, sexual arousal, mating, copulatory performance, inter-copulatory interval, erection, sperm functional parameters, and ultimately, male fertility by enhancing the HPGA axis [38, 39].

4.3 Anti-Oxidative Effects of Medicinal Plants and Male Fertility

Free radicals, such as reactive oxygen species (ROS) like hydrogen peroxide, peroxide, singlet oxygen, superoxide, and hydroxyl radicals, play crucial roles during spermatogenesis, influencing processes like incapacitation, hyperactivation, acrosome reactions, sperm maturation, and sperm/oocyte fusion [44]. The testicular endogenous antioxidant system, comprising nuclear glutathione peroxidase (GP_x), thioredoxin reductase, thioredoxin, superoxide dismutase (SOD), and peroxiredoxin, helps mitigate the damage caused by these active species by scavenging ROS during spermatogenesis [45]. Imbalances in ROS production due to factors like smoking, androgenic-anabolic steroid use, chemotherapy, radiation exposure, infections, and varicocele can deplete the testicular antioxidant system, leading to extensive oxidative damage to biomolecules in cells involved in spermatogenesis, including proteins, nucleotides, polyunsaturated fatty acids, and carbohydrates [46].

Various studies show that exogenous antioxidants can balance the production/scavenging of ROS and minimize oxidative damage to sperm during spermatogenesis. The extracts of plants such as Vaccinium arctostaphylos L., Nasturtium officinale L., Nigella sativa L., Lepidium meyenii L., Garcinia kola L., Ajuga iva L., Vitis vinifera L., Tinospora cordifolia L., Tetracarpidium conophorum L., Vanda tassellata L., Asparagus racemosus L., and Curculigo orchioides L. have been reported to maintain this balance (Table 1)[46-48]. This balance is due to the presence of various polyphenolic compounds (flavonoids and isoflavonoids) such as quercetin, kaempferol, apigenin, proanthocyanidin B1, caftaric acid, cyanidin, chlorogenic, daidzein, biochanin A, formononetin, myricetin and genistein alongside β-carotene, vitamin C, vitamin E, and lipoic acid. These compounds increase the total antioxidant capacity of the testicular tissue by boosting the levels of antioxidant molecules and enzymes, including glutathione (a hydroxyl radical scavenger), glutathione peroxidase (a lipid peroxide scavenger), superoxide dismutase (a superoxide radical scavenger), catalase (a hydrogen peroxide scavenger), which reduce the production of free radicals, including malondialdehyde and nitric oxide [49, 50]. Spermatogenesis and the cell cycles of germinal epithelial cells are continuous processes where the disruption of vital checkpoints will interrupt the normal reproduction and differentiation of sperm [51]. Factors such as decreased levels of the luteinizing hormone (LH) and increased levels of ROS and proinflammatory cytokines inhibit the differentiation and proliferation of spermatogonia, leading to a drop in sperm count and a rise in sperm abnormalities [52].

Studies reveal that extracts from plants like *Anthocleista djalonensis* L. (200 mg/kg/60 days) [25], *Nasturtium officinale* L. (25-100 mg/kg/40 days) [5], *Vaccinium arctostaphylos* L. (100-400 mg/kg/50 days) [8], *Fadogia agrestis* L. (18-100 mg/kg/1-5 days) [26], and *Ruta chalepensis* L. (0.5-2 g/kg/30 days) [27] can induce the HPGA axis (increased LH levels), reduce proinflammatory cytokines (interleukin-6, tumor necrosis factor-α, IL-8, and IL-1β), and neutralize free radicals. These mechanisms support the proliferation and differentiation of spermatogonia in rats and mice.

Herbal antioxidants enhance Sertoli cell activity by increasing water secretion around the spermatogenic lineage and removing toxic substances. Additionally, they elevate testosterone concentration, Leydig cell activity, and sperm motility by facilitating energy (ATP) turnover and inducing Na/K ATPase enzymatic ion pump activity in sperm tails [53, 54].

4.4 Anti-Inflammatory Effects of Medicinal Plants and Male Fertility

Various factors activate inflammatory pathways in the male reproductive system, such as ejaculatory duct obstruction, sexually transmitted infections (e.g., gonorrhea, *Chlamydia*, *Escherichia coli*), urethritis, testicular torsion, varicocele, and inflammation caused by ROS-generating drugs (chemotherapeutics, androgenic-anabolic steroids, and chemical toxins), which can trigger acute and chronic inflammatory cycles [55].

In the male reproductive system, inflammation triggers three compensatory processes: increased capillary permeability, heightened leukocyte migration, and dilation of capillaries to enhance blood flow to the inflamed area [56]. Leukocyte and other inflammatory cell migration fosters a cytokine cascade that diminishes sperm quality by inhibiting the physiological activity of accessory glands, disrupting spermatogenesis, and impeding sperm transfer. Inflammatory cytokines, including TNF-α, IL-1α, IL-1β, and IL-6, are often secreted by macrophages, mononuclear phagocytes, Leydig, and Sertoli cells [53, 57]. These cytokines induce apoptosis, increase inflammatory cell accumulation, disrupt spermatogenesis, suppress Sertoli cell activity, cause edema blockage, elevate ROS production, and ultimately decrease sperm count and motility [58]. *Ginkgo biloba* L. (50 mg/kg/40 days) was found to alleviate male infertility from varicocele and testicular ischemia by reducing pro-inflammatory cytokine production (TNF-α and IL-1β) and enhancing antioxidant enzyme activity, safeguarding normal spermatogenesis during ischemic conditions [13]. *Tinospora cordifolia* L. effectively improved the spermatogenesis cycle, sperm functional parameters, and free radical-scavenging activity in testes. The administration of the plant extract (at a dosage of 1 g/kg for six months) conferred protection against oxidative damage to the testes and sperm in animal models, attributed to the enhancement of antioxidant enzyme activity and reduction in testicular lipid peroxidation [16].

The beneficial effects of anti-inflammatory agents on male fertility can occur through various mechanisms, including reducing vascular permeability, suppressing inflammatory cytokine secretion from phagocytic cells and other leukocytes, protecting parenchymal and nurse cells (Leydig and Sertoli) against apoptosis, and scavenging ROS [59]. A study revealed that *Zingiber officinale* L. extract improved sperm functional parameters by containing flavonoid antioxidant compounds, enhancing endogenous antioxidant pathways, and inhibiting testicular lipid oxidation. Stereological findings also indicated that the extract preserved the normal spermatogenesis cycle by maintaining the germinal epithelium, the integrity of the basement membrane of the seminiferous tubular wall, and the structure of sperm under toxic conditions [18].

4.5 Protective Effects of Medicinal Plants and Male Fertility

Several animal studies mentioned that toxicity with chemicals such as acetamiprid and lead acetate induced testicular injury [59, 60]. Administration of plant extracts of Cyperus esculentus L. (500 and 1000 mg/kg/day for 21 days) to rats exposed to lead acetate [56] shows that these extracts can suppress the cytokine cascade and ultimately increase fertility by reducing the secretion of inflammatory cytokines and the permeability of testicular vessels. Different plant extracts work with the same mechanism. Table 2 shows the name of these plant extracts.

Table 2 Medicinal plant extracts with reducing the secretion of inflammatory cytokines and the permeability of testicular vessels.

References	Plant	Plant part	Dosage used/duration	Animal model	Route of administration	Observed effects
[61]	*Olea europaea* L.		300 mg/kg/day for five days	Rat	Gavage	Improvement of antioxidant indices [increase of heme oxygenase-1 (HO-1) and nuclear factor erythroid 2-related factor (Nrf2)] and SOD, CAT, glutathione peroxidase (GSH-Px), and glutathione reductase (GSH-R) activities ($p < 0.05$) Improvement of inflammatory indicators (reduction of TNF-α and IL-1β) ($p < 0.05$)
[62]	*Tiliacora triandra* L.		100 and 400 mg/kg/day for 30 days	BALB/c mice	Gavage	Improvement of antioxidant indices increased SOD, CAT, and GSH-Px ($p < 0.05$) Improving the level of T, LH, and FSH, sperm parameters ($p < 0.05$)
[63]	*Origanum vulgare* L.		100, 200, and 400 mg/kg/day for five wk	BALB/c mice	Gavage	Improvement of antioxidant indices increased SOD, CAT, and GSH-Px ($p < 0.05$) Improving the level of T, LH, and FSH, sperm parameters ($p < 0.05$) Improvement of inflammatory indicators (reduction of IL-6, TNF-α, IL-1β) ($p < 0.05$)
[64]	*Coffea arabica* L.		50 and 100 mg/kg for four wk	Rat	Gavage	Improvement of antioxidant indices increased SOD, CAT, and GP_x ($p < 0.05$) Improving the level of T, LH, and FSH, sperm parameters ($p < 0.05$) Improvement of apoptosis and inflammatory indicators (reduction of IL-1β, TNF-α, Bax, and caspase-3) ($p < 0.05$)

[65]	*Shorea roxburghii* L.	400 mg/kg for four weeks	Rat	Gavage	Improvement of antioxidant indices increased SOD, CAT, and GP_x ($p < 0.05$) Improving the level of T, LH, and FSH, sperm parameters ($p < 0.05$) Improvement of apoptosis and inflammatory indicators (reduction of IL-6, TNF-α, p38 MAPK) ($p < 0.05$)
[25]	*Anthocleista djalonensis* L	200 mg/kg/day for 60 days	Rat	Gavage	Improvement of antioxidant indices increased SOD, CAT, and GP_x, as well as decreased NO levels ($p < 0.05$) Improvement of inflammatory indicator (reduction of IL-6) ($p < 0.05$)
[66]	*Cordyceps cicadae* L.	50-400 mg/kg/day for seven days	Rat	Intraperitoneal injection	Improvement of antioxidant indices, increased SOD, CAT, and GP_x, as well as decreased MDA ($p < 0.05$) Improving the level of T, LH, and FSH, sperm parameters ($p < 0.05$) Improvement of apoptosis and inflammatory indicators (reduction of IL-6 and TNF-α) ($p < 0.05$)
[67]	*Ginkgo biloba* L.	100 mg/kg/day for 10 days	Rat	Intraperitoneal injection	Improvement of antioxidant indices, increased SOD levels and decreased MDA levels ($p < 0.05$) Improving the level of T ($p < 0.05$) Improvement of apoptosis and inflammatory indicators (reduction of IL-1β, TNF-α, Bax, NF-κB , p53, and caspase-3) ($p < 0.05$)
[68]	*Moringa oleifera* L.	500 mg/kg/day for 60 days	Rat	Gavage	Improvement of antioxidant indices, increased SOD, CAT, and GP_x, as well as decreased MDA ($p < 0.05$)

						Improving the level of T levels ($p < 0.05$)
[69]	*Brassica oleracea L.* and *arum carvi* L	Leaf	Broccoli (200 and 300 mg/kg)-caraway (200 and 300 mg/kg) For 42 days	Mice	Gavage	Improving sperm parameters (diameter and number of spermatogonium, primary spermatocytes, spermatids, and sperm count) ($p < 0.05$) Improving antioxidant indices (increasing SOD and CAT activity and decreasing MDA and DNA fragmentation) ($p < 0.05$)
[70]	*Origanum vulgar L.*	Leaf	25, 250 and 500 mg/kg for 10 days	Rat	Intraperitoneal injection	Improvement of testis cell parameters (Sertoli, spermatogonia, spermatocytes, and Leydig cells) ($p < 0.05$) Improving antioxidant indices (reducing MDA level) ($p < 0.05$)
[71]	*Zingiber officinale Roscoe L.*	Whole prats	250 mg/kg for 28 days	Rat	Gavage	Significant increase in T, L, and FSH levels ($p < 0.05$) Improvement of antioxidant and inflammatory parameters StAR, P450scc, 17βHSD, Nrf-2 and NF-κB ($p < 0.05$) Reduction in MDA and TNF-α levels ($p < 0.05$)
[72]	*Artemisia annua L.*		100 mg/kg/8 weeks	Rat	Gavage	Treatment of obesity-related testicular dysfunction showed the restoration of hormonal imbalance ($p < 0.05$)

5. Conclusions

Pro-drugs derived from herbs, with fewer side effects and more comprehensive effects than chemical drugs, are available to the public at considerably lower costs. Among various plants affecting male fertility, those with a high content of aphrodisiac compounds (such as *Kaempferia parviflora* L., *Epimedium brevicornum* L., *Terminalia catappa* L., *Syzygium aromaticum* L., *Pfaffia paniculata* L., *Chlorophytum borivilianum* L., and *Fadogia agrestis* L.) can increase serum testosterone concentration, libido, and sexual vigor and improve premature ejaculation, low libido, and erectile dysfunction. The compounds present in some other plants (such as *Morinda officinalis* L., *Zingiber officinale* L., *Anthocleista djalonensis* L., *Nasturtium officinale* L., *Vaccinium arctostaphylos* L., and *Fadogia agrestis* L.) also increase the levels of LH and testosterone by amplifying the HPGA axis in infertile men, leading to the proliferation and differentiation of primary spermatogonia. These compounds regulate spermatogenesis cycles and ultimately increase sperm differentiation in men with low sperm counts. Plants with a high content of polyphenolic compounds such as flavonoids and isoflavones (e.g., *Annona muricata* L., *Ginkgo biloba* L., *Apium graveolens* L., *Butea superba* L., *Vaccinium arctostaphylos* L, and *Ruta chalepensis* L.) can protect the structure and physiological activity of testicles against oxidative damage, elevating the chances of early fertilization and implantation of embryos in the uterus. Some plants (such as *Ginkgo biloba* L., *Vaccinium arctostaphylos* L., *Anthocleista djalonensis* L., *Fadogia agrestis* L. *Ruta chalepensis* L., and *Zingiber officinale* L.) containing compounds with anti-inflammatory and anti-apoptotic properties can inhibit the expression of pro-inflammatory cytokines and pro-apoptotic genes (i.e., suppressing endogenous and exogenous apoptotic pathways) and finally protect germinal epithelial spermatogonia cells against apoptosis induced by immune mediators. Based on the findings of this review, it can be concluded that the majority of plants utilize multiple protective mechanisms (such as antioxidant, anti-inflammatory, anti-apoptotic, Hypothalamic-Pituitary-Gonadal Axis promoting, and aphrodisiac properties) to enhance sexual performance. These properties, tailored to the type of infertility, could potentially be beneficial in the treatment of infertile men.

Author Contributions

Mohsen Akbaribazm participated in performance of the research, research design and writing of the paper. Elnaz Khordad and Mohsen Rahimi participated in data analysis and writing of the paper.

Competing Interests

Authors declare that there is no conflict of interest.

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