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Review Article

Modern possibilities of phytotherapy for male infertility from the standpoint of evidence-based medicine

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Abstract

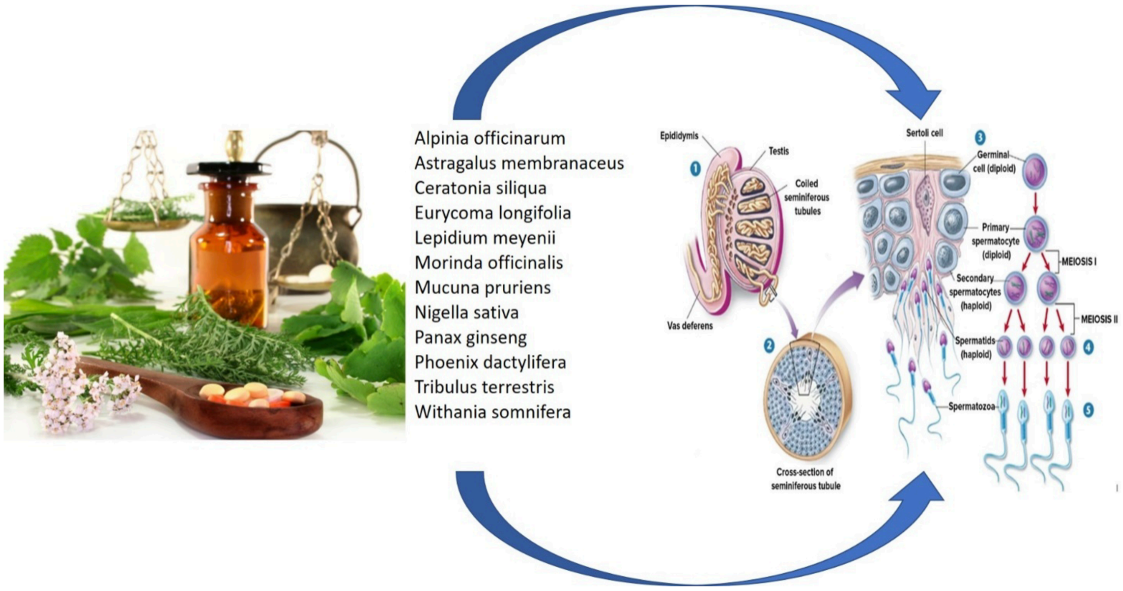
Introduction: Male infertility is an topical medical and social problem of modern reproductive medicine. Its pharmacotherapy is often empirical in nature, and the most popular method remains the use of various herbal substances (phytotherapy), the effectiveness of which remains still understudied in the framework of evidence-based medicine.

Materials and Methods: The results of research, thematic, systematic and Cochrane reviews and meta-analyses were searched in Medline/PubMed medical databases over the past 5 years using the search queries "plants male infertility", "plants sperm", "phytotherapy male infertility", "phytomedicinal therapeutics male infertility", "systematic review", "meta-analysis", and "review".

Results: The vast majority of herbal substances offered for the treatment of male infertility demonstrate insufficient or contradictory evidence base for their clinical effectiveness, although some of them can be very useful pharmacotherapeutic options in the combined therapy of male infertility.

Conclusion: Not all plant substances with a "reproductive effect" positioned in them actually have proven reproductive effects in studies in humans, therefore, the choice of phytotherapeutic agents in the treatment of idiopathic male infertility should be currently approached extremely carefully, especially in cases when we choose phytotherapy as an option for empirical monotherapy of male reproductive disorders.

Graphical Abstract



Keywords

male infertility, medicinal plants, phytotherapy, herbal agents, efficacy, meta–analysis, systematic review

Introduction

About half of all cases of familial infertility have a male factor, which is the sole cause of infertility in 20-30% of cases (Salonia et al. 2022). Many conditions can affect a man's fertility, including congenital or acquired urogenital abnormalities, exposure to gonadotoxins (drugs, radiation therapy, or chemotherapy), malignant neoplasms, urogenital tract infections, elevated scrotal temperature (for example, from varicocele), endocrine disorders, genetic abnormalities, and immunological factors. Even after a thorough examination of a man, no pathology is discovered in approximately 30–40% of cases, which could account for the abnormality in one or more spermogram parameters. Historically, this type of reproductive disorder is called idiopathic male infertility (Salonia et al. 2022). Currently, it is believed that idiopathic male infertility may be associated with a number of pathological factors that have not yet been identified as proven reproductive disruptors (Salonia et al. 2022). Even after a thorough examination of a single infertile man, the mechanisms underlying the reproductive disorders that cause idiopathic male infertility remains unknown. As a result, pharmacotherapy for idiopathic male infertility is empirical rather than pathogenetically substantiated, presuming the use of various pharmacological agents with expectedly positive effects on male fertility. Regretfully, there is not much high-level evidence of the safety or effectiveness of these drugs for reproduction. Many experts believe that empirical treatment, which can be categorized as hormonal (gonadotropins, antiestrogens, aromatase inhibitors, dopamine receptor agonists, etc.), non-hormonal (vitamins, trace elements, antioxidants, antibiotics, NSAIDs, angioprotectors, etc.), or surgical (with varicocele or abnormalities of the reproductive system), could be appropriate for idiopathic male infertility before the use of assisted reproductive methods (García-Baquero et al. 2020; Wei et al. 2021; Li et al. 2022). Although there are currently few large randomized and controlled clinical trials to support the efficacy of different treatments for idiopathic male infertility, recent systematic reviews and meta-analyses demonstrate that treatment with gonadotropins, antiestrogens, and antioxidants/vitamins improves sperm parameters in men with idiopathic pathospermia and increases the frequency of pregnancy and live births in a couple (Cannarella et al. 2019; Smits et al. 2019; Shahid et al. 2021; de Ligny et al. 2022).

The use of various regulators of spermatogenesis of plant origin (phytotherapy) is one of the oldest, but still widely used, approaches to modern empirical pharmacotherapy of male infertility. Medicinal plants have been used for centuries in the folk medicine of many different countries and peoples around the world to treat and prevent a wide range of human diseases. Research on the possible impact of different extracts from medicinal plants on male reproductive function is still ongoing. This review aims to provide an overview of the most studied and frequently mentioned plant substances in the scientific literature over the last 5 years that have an

impact on male reproductive function from the standpoint of evidence-based medicine.

The aim of this review is to describe and systematize modern scientific data on the effect of the most studied and frequently mentioned plant substances on male reproductive function in the scientific literature over the last 5 years from the standpoint of evidence-based medicine.

Materials and Methods

Using the search queries "plants male infertility", "plants sperm", "phytotherapy male infertility", "phytomedicinal therapeutics male infertility", "systematic review", "meta-analysis", and "review," researchers searched the English-language medical databases Medline/PubMed for the results of clinical and experimental studies, thematic, systematic, and Cochrane reviews, as well as meta-analyses, over the last five years.

Results

Phytotherapy, which involves various active ingredients and extracts from well-known herbs, has been shown to positively impact male fertility factors, testosterone production, and sexual behavior based on available *in vivo* and *in vitro* studies (Ramgir et al. 2022). The effectiveness of phytoactive substances depends on the methods of their preparation and forms of consumption, including decoctions, extracts, semi-purified compounds, etc.

The potential mechanisms behind the beneficial effects of plant raw materials on male reproductive parameters vary, depending on a specific plant. However, certain universal mechanisms of phytotherapy's influence have been described, including the stimulation of spermatogenesis through activation of the testosterone signaling pathways in the gonads, reduction of oxidative stress of spermatozoa (antioxidant effect), inhibition of chronic inflammation in the gonads (anti-inflammatory effect), activation of particular signaling pathways in the gonads (e.g. extracellular signal-regulated kinase (ERK)/ protein kinase B (PKB)/transforming growth factor–β1 (TGF–β1)/nucleus factor kappa-light-chain-enhancer of activated B cells (NF–kB), as well as an indirect effect on sexual behavior(the effect of aphrodisiacs) (Ramgir et al. 2022).

Nowadays, it has been shown that the active ingredients and crude extracts of numerous medicinal plants, such as Lepidium meyenii, Rupus coreanus, Tribulus terrestres, Panax ginseng, Petasites japonicas, Apium graveolens, Eurycoma longifolia, Pedalium murex, Corchorus depressus, Mucuna pruriens, Astragalus membranaceus, Nigella sativa, Crataegus monogyna, Fagarates smannii, Phaleria macrocarpa, Anacyclus pyrethrum, Cynomorium songaricum, and Morinda officinalis have influenced fertility in both laboratory animals and in vitro studies as well as in clinical human studies. These include antioxidant, anti-inflammatory, stimulating spermatogenesis and libido, relaxing the smooth muscles of the seminal tract, and androgenic effects of these herbal substances (Abarikwu et al. 2020).

Several active chemical compounds, including glucosinolates, antocianins, proantocianidins, protodioscin, ginsenosides, sesquiterpenes, phytoestrogens, quasinoids, diosgenin, thymoquinone, flavonoids, alkaloids, and glycosides secreted from these plants, have targeted effects on gonads, but their use in clinical practice remains limited. Apparently, there are still many extracts of medicinal plants that have not been characterized to identify unique phytochemicals that target gonads and spermatogenesis. In addition, in light of the current crisis of male fertility, efforts are justified to select candidates for pro-treatment from medicinal plants for further research at the molecular-cellular level in order to clarify the mechanisms of their clinical effect on testicular function (Abarikwu et al. 2020).

Many active chemicals that are extracted from these plants, such as flavonoids, alkaloids, glycosides, ginsenosides, ginsenosides, sesquiterpenes, phytoestrogens, quassinoids, diosgenin, thymoquinone, and flavonoids, have specific effects on the gonads, but their application in clinical practice is still restricted. It seems that a lot of medicinal plant extracts are still uncharacterized, making it difficult to pinpoint the special phytochemicals that affect spermatogenesis and the gonads. Furthermore, considering the present male fertility crisis, it is appropriate to choose pro-drug candidates from medicinal plants for additional molecular-cellular research to better understand the mechanisms underlying their clinical impact on testicular function (Abarikwu et al. 2020).

More than 90 phytochemical components, many of which are phenolic compounds, are presented in ***Alpinia officinarum***. Of these, diarylheptanoids, which are extracted from the rhizome and are thought to be the most biologically active components, have shown in both *in vitro* and in vivo studies a wide range of biological activity, including anti-inflammatory, antibacterial, antiviral, antioxidant, antitumor, cytotoxic, osteoprotective, and hypolipidemic effects (Pillai et al. 2018).

In Kolangi F et al.'s (2019) prospective clinical double-blind placebo-controlled study, 76 men with idiopathic infertility were split into two groups: group 1 received treatment with capsules containing a dry extract of *Alpinia officinarum* root at a daily dose of 300 mg (n=31); group 2 received a placebo (n=29) for a period of 12 weeks (Kolangi et al. 2019).In contrast to group 2, which showed no changes, after 12 weeks of treatment, the total number of spermatozoa and the number of spermatozoa with normal morphology increased in group 1 from $52\times10^6\pm24\times10^6$/mL to $71\times10^6\pm23\times10^6$/mL ($p=0.043$) and from 14.34%±9.16% to 19%±14.89% ($p<0.001$), respectively. No side effects were observed (Kolangi et al. 2019).

According to Heidari H. et al.'s (2021) experimental study, rats with streptozocin–induced diabetes mellitus had significantly lower body weights, testicular weights and volumes, and worse sperm parameters. They also had significantly lower serum testosterone and follicle-stimulating hormone (FSH) levels than the control group, which consisted of healthy animals ($p<0.05$). These animals' testosterone levels and sperm parameters improved significantly ($p<0.05$) after injection of *Alpinia officinarum* extract at a dose of 500 mg/kg. Additionally, morphological examination of the testes revealed that the germinogenic epithelium thickness and seminal tubule diameter were larger in the treated group than those of the placebo group ($p<0.05$) (Heidari et al. 2021).

Astragalus membranaceus is a well-known representative of traditional Chinese phytomedicine with

a long history of clinical application. Astragalus polysaccharides and compounds of flavonoids, saponins, alkaloids, etc. are the main constituents. These compounds have a wide range of pharmacological effects and hold great potential for the development of different drugs, such as the ground-breaking telomerase activator (TA–65), which represents a new avenue in molecular anti-aging medicine. Nowadays, Astragalus is known to have a variety of pharmacological effects, including immune and cytokine regulation, anti-aging, antitumor, antiviral, hypoglycemic, hypolipidemic, antifibrotic, antimicrobial, antioxidant, and radioprotective (Zheng et al. 2020). A recent experimental study using 47 male Wistar rats has been conducted to study the anti-aging effects of *Astragalus membranaceus* (TA–65 medication) and pomegranate extract. The rats were divided into groups: young rats, aging rats, aging rats treated with TA–65 (500 mg/kg/day), and aging rats treated with pomegranate extract (250 mg/kg/day) (Alshinnawy et al. 2020). Treatment with TA–65 or pomegranate effectively reduced the severity of age-related male fertility disorders by restoring hormonal balance and testicular architecture. Comparing the therapeutic outcomes, it was discovered that taking TA-65 significantly increased the dynamics of improvement in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels and sperm abnormality parameters compared to the pomegranate extract treatment (Alshinnawy et al. 2020). Another experimental study showed that *Astragalus membranaceus* extract had a positive effect on the normalization of immunity, cytokine metabolism, and spermatogenesis in testicular tissue in a model of cyclophosphamide-induced orchipathy in male mice (Qiu et al. 2019).

Ceratonia siliqua is one of the most widely used medicinal plants in the Mediterranean region. It was traditionally grown for its unique seeds, which functioned as the "carat," a unit of measurement in jewelry. Many studies conducted over the past 50 years have identified a wide range of phytocomponents (phenolic compounds, flavonoids, tannins, anthocyanins, alkaloids, glycosides, proteins, and minerals) present in all parts of Ceratonia siliqua. Plant extracts have been shown to possess antioxidant, antiproliferative, hepatoprotective, antibacterial, antifungal, anti-inflammatory, antidiabetic, and neuroprotective properties (Lakkab et al. 2018). Numerous studies conducted in the last five years have demonstrated the efficacy of this plant's extracts in the treatment of male infertility. Therefore, the aim of a recent prospective clinical study was to assess the positive effects of *Ceratonia siliqua* extract on ejaculate parameters as well as the quality of sperm chromatin following thawing in 40 normozoospermic samples. Each set was divided into ten groups. In the first to the fifth groups, *Ceratonia siliqua* was added to the freezing medium at concentrations of 0 (as a control group), 5, 10, 20, and 30 μg/mL. In the sixth to tenth groups, similar concentrations of plants were added to the thawing medium and incubated for 30 minutes. The results showed that *Ceratonia siliqua* extract at concentrations of 10 and 20 μg/mL in the freezing/thawing medium significantly increased the progressive mobility, normal morphology, and viability of spermatozoa after thawing ($p<0.05$). Furthermore, a much more marked improvement in reproductive parameters was observed with the dose of 20 μg/mL compared with the dose of 10 μg/m ($p<0.05$) (Faramarzi et al. 2019). Male mice exposed to cyclophosphamide or lead showed a decrease in the number and viability of spermatozoa, an increase in the number of abnormal spermatozoa against the background of an increase in the level of malondialdehyde in testicular tissue ($p<0.05$) and an increase in the number of spermatozoa with damaged DNA. However, these disorders were significantly restored ($p<0.05$) when *Ceratonia siliqua* extract was administered ($p<0.05$) (Soleimanzadeh et al. 2020; Mehraban et al. 2021).

Furthermore, studies conducted on mice with a laboratory model of azoospermia have demonstrated a significant improvement in spermatogenesis against the background of treatment with *Ceratonia siliqua* extract. This suggests, according to the authors, that the plant has an anti-apoptotic and inductive role in the gene expression regulating the cell cycle of spermatogenesis involving Sertoli and Leydig cells ($p<0.05$). Because of this, this plant holds great promise for treating azoospermia, especially those brought on by cancer and the side effects of chemotherapy (Ghorbaninejad et al. 2023).

A randomized controlled clinical trial by Aghajani et al. (2021) included 60 infertile men with oligozoospermia, asthenozoospermia, and teratozoospermia (Aghajani et al. 2021). The participants were randomly divided into 2 groups: group 1 received 1500 mg of *Ceratonia siliqua* syrup daily, group 2 received 200 mg of vitamin E daily for 3 months. After 3 months, the ejaculate quality indicators in group 1 were significantly better than in group 2; however, there was no significant difference in hormonal parameters and markers of oxidative stress between both groups, except for the overall antioxidant capacity, which was higher after treatment in group 1, along with a higher number of pregnancies (Aghajani et al. 2021). In contrast, other researchers have shown that oral administration of *Ceratonia siliqua* capsules at a daily dose of 1500 mg for 90 days improves only sperm motility, but does not have a significant effect on their morphology and quantity compared to taking vitamin E capsules (Sanagoo et al. 2021).

Eurycoma longifolia is a shrub of the Simarubaceae family, native to Southeast Asia, which has long been known by various names as a means to strengthen male sexual health and an aphrodisiac, especially in oriental medicine (Tongkat Ali, or Malaysian ginseng (Malaysia), Tung Sava (Thailand), PasakBumi (Indonesia), Kay Ba Binh (China), etc.) (George et al. 2014). The composition of the plant is rich in biologically active components, the most prevalent of which are quassinoid triterpenoid compounds, specifically eurycomanone, and eurycomanol. Many *in vivo* animal studies and human clinical trials have been carried out worldwide in the last few decades to investigate the potential benefits of *Eurycoma longifolia* in the treatment of low libido, male infertility, erectile dysfunction, and testosterone deficiency. According to a number of investigators, *Eurycoma longifolia* is a safe and natural alternative for testosterone replacement therapy (TRT) that improves men's sexual health, bone health, physical condition, glycemic profile, and may even have a preventive effect on prostate cancer (Jayusman et al. 2018; Ezzat et al. 2019; Tsaiet al. 2020; Chanet al. 2021). The use of this phytobooster was found to be significantly and reliably correlated with positive treatment outcomes for male sexual disorders in 7 out of 11 randomized placebo-controlled studies, multiple cohort studies, and pilot studies conducted between 2000

and 2014; the remaining 4 studies were unable to show a significant impact on male sexual health (Thu et al. 2017). The effect of *Eurycoma longifolia* on male reproduction has not been sufficiently studied, although experimental studies demonstrate its protective effects on ejaculate freezing procedures, as well as the ability to improve spermatogenesis in laboratory models of oligozoospermia (Baiee et al. 2018; Chung et al. 2021).

Lepidium meyenii is an edible root vegetable of a plant native to the Andean region of Peru. The nutritional and therapeutic properties of the plant have led to its use as a dietary supplement for centuries. *Lepidium meyenii* is rich in important nutrients and highly biologically active secondary metabolites, such as macaridine, macamides, and glucosinolates. Using research published between 2000 and 2019, a systematic review of the PubMed medical databases found numerous studies that consistently showed *Lepidium meyenii* to have a beneficial impact on men's sex hormone levels, sexual behavior, and the quantity and quality of ejaculate (Tafuri et al. 2021).In a double-blind, randomized, placebo-controlled pilot study, 69 men with asthenozoospermia and/or oligozoospermia who received *Lepidium meyenii* at a dose of 2 g/day (n=35) or placebo (n=34) for 12 weeks saw a significant difference in sperm concentrations (prior to treatment: 15.04±5.61 versus after treatment: 10.16±3.59; p=0.011), but not in other spermogram characteristics when compared to the placebo group. A double-blind randomized placebo-controlled pilot study in 69 men with asthenozoospermia and/or oligozoospermiawho received *Lepidium meyenii* at a dose of 2 g/day (n=35) or placebo (n=34) for 12 weeks, showed that administration of *Lepidium meyenii* led to a significant difference in sperm concentrations (before treatment 15.04±5.61 versus 10.16±3.59 after treatment, respectively; p=0.011), but not in other spermogram characteristics when compared to the placebo group (Alcalde et al. 2020). Clinical and experimental studies have also shown that taking *Lepidium meyenii* significantly reduces the frequency of sperm DNA fragmentation, activates the acrosome reaction of spermatozoa and protects spermatogenesis from the negative effects of various gonadotoxins (Aoki et al. 2018; D'Anza et al. 2021; Greco et al. 2021).

It should be noted that *Lepidium meyenii* is one of the very few plants for which two meta-analyses of its effects on reproduction have been performed. The initial and most recent one included three RCTs (randomized clinical trials) and two uncontrolled observational studies that were found by searching through eleven databases between the time of their creation and March 2016. *Lepidium meyenii* has been shown in one RCT to improve sperm motility in infertile men. Two other RCTs showed a positive effect of *Lepidium meyenii* on some parameters of ejaculate quality in healthy men. Furthermore, the plant may improve ejaculate quality, according to two uncontrolled observational studies (Lee et al. 2016).

Based on a search across nine databases of randomized controlled trials (RCTs), the second meta-analysis of 2022 has already turned up five RCTs, three of which demonstrated the equivocal effectiveness of *Lepidium meyenii* on ejaculate parameters in infertile men. Consequently, their meta-analysis was unable to definitively determine the reproductive effectiveness of *Lepidium meyenii* in comparison to a placebo. Two other RCTs also showed a contradictory effect of *Lepidium meyenii* on several parameters of ejaculate quality in healthy men. Thus, more research is needed to determine the exact impact of *Lepidium meyenii* on the quality of ejaculates in both infertile and healthy men, as indicated by the data from meta-analyses (Lee et al. 2022).

For a very long time, ***Morinda officinalis*** has been used in traditional Chinese and Northeast Asian medicine as a tonic to strengthen bones, boost immunity, and improve kidney function. It is also used to treat a variety of inflammatory diseases, depression, infertility, and sexual dysfunction.More than 100 chemical compounds have been isolated from this plant, the main components of which are polysaccharides, oligosaccharides, anthraquinones, and iridoid glycosides (Zhang et al. 2018). Over the past five years of experimental research, extracts from this plant have demonstrated a protective effect on male rats suffering from spermatogenesis disorders linked to varicocele and its progression (Zhu et al. 2019; Ding et al. 2021). It is still unclear and unexplored how beneficial this plant is for male reproductive disorders.

Mucuna pruriens belongs to the Fabaceae and is known as velvet bean (Kawaanch in Hindi). The composition of the *Mucuna pruriens* includes levodopa (a precursor of dopamine and the main component of its beans, eventually turn into adrenaline), as well as mucunain (which causes skin itching upon contact), nicotinic acid, tetrahydroisoquinoline alkaloids, serotonin and its precursor 5–hydroxytryptophan, various saponins, anthraquinones, flavonoids, terpenoids, cardiac glycosides and tannins, coenzyme Q10 and nicotinamide adenine dinucleotide (NADH), inositol, trace elements (selenium, iron and magnesium). This plant has shown anticholesterolemic, antiparkinsonian, antioxidant, antidiabetic, anti-inflammatory, antimicrobial, antitumor activity, and is also considered as an aphrodisiac (Pathania et al. 2020).

The *Lepidium meyenii* seed extract has been shown to have strong antioxidant properties, significantly increases spermatozoa concentration (while having no effect on other spermatogenesis parameters), and to upregulate the expression of AKAP4 protein, androgen receptors, and the testicular protein TyrPho in spermatozoa (Iamsaard et al. 2020). *Lepidium meyenii* extract significantly lowered cortisol levels in an experimental model of chronic stress, protected sperm parameters and reproductive tissues from damage, delayed the spermatozoa's premature acrosome reaction, and increased the expression of the testicular steroidogenesis proteins CYP11A1, AR, and HSP70 while lowering caspase expression. These results open the door to using this plant as an alternative medication to treat male infertility (Choowong-In et al. 2021; Lapyuneyong et al. 2022).

Nigella sativa is a plant of the Ranunculaceae. This plant has long been known for its healing qualities, which show up in relatively small doses and do not require any special preparation for the seeds. The chemical composition of black cumin is quite complex; its most studied and active components are the alkaloids thymoquinone, nigellidine and nigellicine, which are especially abundant in black cumin seed oil. Thorough studies of clinical effects of its main component, thymoquinone, from 1979 to 2015, convincingly demonstrated that over the past few decades, the antibacterial, antiproliferative, proapoptotic, anti-inflammatory, hypoglycemic, hypolipidemic, endothelium-protective, neuroprotective, anti-atherogenic, and

antiepileptic properties of this compound have been revealed in animal studies both *in vivo* and *in vitro* (Gholamnezhad et al. 2016).

In clinical studies, black cumin has demonstrated antimicrobial, antioxidant, anti-inflammatory, antitumor and antidiabetic properties, as well as therapeutic effects on metabolic syndrome, gastrointestinal, neuronal, cardiovascular, respiratory, urinary, and reproductive disorders (Ahmad et al. 2013).Thymoquinone may be able to enhance steroidogenesis and spermatogenesis as well as to have a positive impact on prostate health, according to some convincing evidence that has recently started to emerge. These findings, however, were primarily derived from experimental studies. Therefore, black cumin oil and metformin together could provide novel possibilities for the treatment of obesity-related infertility (Leisegang et al. 2021).Thymoquinone has also been demonstrated in experimental studies to play a protective role in ejaculate freezing procedures as well as in maintaining and restoring spermatogenesis under the influence of various gonadotoxins (Mabrouket al. 2016; Umar et al. 2017; Mosbah et al. 2018; Salahshooret al. 2018; Alghamdi et al. 2020; Uchendu et al. 2021).

Panax ginseng is a perennial medicinal plant belonging to the Araliaceae. It got its name from the similarity of its root to a human body and literally means "human root". Polyacetylenes and triterpene glycosides, also known as saponins (ginsenosides), are the primary active ingredients in Panax ginseng. These compounds are found in the plant's leaves, petioles, stem, and small adventitious roots. Its root, which has over a hundred distinct ginsenosides, is the traditional raw material for medicine. In laboratory models of the effects of various gonadotoxins, Panax ginseng has shown a positive effect on steroidogenesis. This effect is attributed to Panax ginsenosides' antioxidant properties and support for the synthesis of nitric oxide (NO)in the neurotelium and endothelial vessels, where Panax ginsenosides act as biochemical donors or precursors. Simultaneously, this has a positive effect on sexual and reproductive function (Ganjkhaniet al. 2019; Kuet al. 2020; Li et al. 2021; Shan et al. 2021). Nevertheless, not all of these effects have strong clinical study support. Furthermore, the literature that is currently available contains no studies on the effects of Panax ginseng on human reproduction. The primary cause of the lack of reliable systematic reviews and meta-analyses evaluating its effects on male reproduction is that in 2018, a protocol was created for a future systematic review, but it has not been published yet (Lee et al. 2018).

***Phoenix dactylifera*.** The phoenix palm is regarded as one of the oldest fruit crops in the world and is cultivated primarily for its highly nutritious fruits, which are staple foods in many nations, particularly those around the Persian Gulf. Dates are rich in organic acids, phenols, flavonols, carotenoids, minerals, and vitamins, among other bioactive and functional compounds. Descriptive reviews of experimental studies indicate that date palm pollen exhibits gonadotropic and spermatogenic activity, protects spermatogenesis from various chemical gonadotoxins, and positively affects liver function, sex steroid hormone balance, cholesterol, lipids, total protein, albumin, globulin, reduces the severity of oxidative stress, and lipid peroxidation reactions in male rats (Tahvilzadeh et al. 2016). Nonetheless, there are not many clinical studies on the date palm's ability to treat male infertility. However, there are very few clinical trials of the effectiveness of date palm in male infertility.

The single meta-analysis of research on the impact of pollen, seed powder, and date palm extract on male reproduction that was published in Turkish and English between 2005 and 2016 revealed that there are very few randomized controlled trials (RCTs).Despite this, the study found that date palm components positively change male fertility-regulating hormones, increase sperm motility, and increase testicular and epididime mass due to their high antioxidant activity, which is predicated on the presence of phenolic compounds in the composition. Furthermore, the gonadotropic and steroid components found in date palm pollen play an important role for protecting men's spermatogenesis (Tatar et al. 2018).

Tribulus terrestris is an annual plant of the Zygophyllaceae family. It is a widely distributed plant that has adapted to survive in dry climates. The composition of the plant includes protodioscin, usually acting as the main bioactive compound (up to 45% of the composition), dioscin, diosgenin, tribulosin, pseudoprotodioscin, protodibestin, tribestin, spirostanol, furostanol, and other active phytosubstances. Pharmaceutical manufacturing companies have historically positioned *Tribulus terrestris* as an effective testosterone phytobooster in sports medicine.However, a meta-analysis in 2014found that while some animal studies demonstrated a significant increase in serum testosterone levels following Tribulus terrestris administration, human studies only showed this effect when the plant was included in complex supplements. The available literature on the effectiveness of the plant in increasing the human testosterone level is very limited and indicates that *Tribulus terrestris* is ineffective for this purpose; therefore, marketing statements are unfounded (Qureshi et al. 2014). The use of *Lepidium meyenii* and *Tribulus terrestris* to raise serum testosterone levels in men has not been scientifically proven, according to a targeted literature search that included studies published in the Cochrane, PubMed, and Web of Science databases between 2002 and 2018 (Santos et al. 2019). In men with idiopathic infertility, *Tribulus terrestris* may improve ejaculate parameters, although there is conflicting evidence regarding its efficacy as a testosterone booster (Santos et al. 2019). Moderate evidence supports the use of *Eurycoma longifolia*, *Mucuna pruriens*, *Withania somnifera*, *Trigonella foenum-graceum* and *Nigella sativa*seeds to increase total testosterone and improve reproductive parameters in men (Santos et al. 2019). Data with moderate evidence indicate an increase in total testosterone and an improvement in the spermogram when using 5000 mg/day of powdered seeds of *Mucunapruriens* and *Withania somnifera* root during a 12–week period in patients with oligozoospermia (Santos et al. 2019). While there is conflicting evidence to support the use of *Serenoa repens* to improve prostate health, there is more positive and encouraging data to support the benefits of *Pygeum africanum*, *Urtica dioica*, β-sitosterols, extracts of pollen, onions, garlic, and tomatoes (Santos et al. 2019). In a systematic review that included seven studies on inclusion criteria, Sanagoo et al. (2019) found that, while six other studies reported that *Tribulus terrestris* was effective in improving some or all sperm parameters, only one quasi-experimental study without a control group reported that the plant was ineffective in treating idiopathic male infertility (Sanagoo et al. 2019).

Indian root ***Withania somnifera*** is used as an adaptogen in Ayurveda and has been valued for its unique medicinal properties for thousands of years. The active components of *Withania somnifera* include saponins, phytosterols, alkaloids, phenolic acids, peptides, lipids, various micro- and macroelements, sitoindosides, lactones, coumarin glycosides, etc. Over the past five years, descriptive literature reviews have demonstrated that *Withania somnifera* significantly enhances the function of the reproductive system through a variety of mechanisms, chiefly by elevating enzymatic activity and lowering oxidative stress in seminal plasma. Furthermore, its extract enhanced the release of LH and FSH, resulting in the stimulation of gametogenesis and an enlargement of the gonads in females; however, concurrent experimental investigations revealed that *Withania somnifera* possessed a reversible spermicidal effect on male animals (Nasimi et al. 2018).A systematic search was conducted using the PubMed/MEDLINE, EMBASE, Scopus, Cochrane Library, and DHARA databases to objectively evaluate the safety and efficacy of *Withania somnifera* in infertile men. The results included one observational and four randomized clinical trials (Durg et al. 2018). Data that were systematically analyzed showed that after taking *Withania somnifera* for 90 days, men with oligospermia had a statistically significant ($p \leq 0.002$) increase in their sperm concentration (167%), ejaculate volume (59%), and motility (57%).A meta-analysis of observational studies revealed that the administration of *Withania somnifera* significantly improved the parameters of the ejaculate (volume: mean difference [MD], 0.28 mL; 95% confidence interval [CI], 0.12 to 0.43; $p=0.0004$; sperm concentration: MD, 13.57 million/mL; 95% CI from 11.12 to 16.01; $p<0.00001$; sperm motility: MD, 8.50%; 95% CI from 7.36 to 9.63; $p<0.00001$), and in couples with normozoospermic men, there was a 14% chance of a successful pregnancy outcome. The results of the meta-analysis also showed a significant improvement in the hormonal profile of blood serum, oxidative biomarkers, and antioxidant vitamins in seminal plasma during treatment with *Withania somnifera* without any side effects. Thus, despite being highly positive, the available data on the effectiveness of *Withania somnifera* in treating male infertility are insufficiently reliable due to the lack of evidence-based studies. Therefore, more high-quality randomized controlled trials are needed (Durg et al. 2018).

Discussion

The analysis of the evidence supporting the efficacy of the most widely used plant raw materials in practical medicine to enhance male fertility revealed a marked lack of high-quality RCTs and an extremely heterogeneous set of data. Referencing thorough systematic reviews and meta-analyses from the previous five years is necessary in order to summarize the data acquired and provide a comprehensive overview of the studies that have been carried out.

Therefore, one of the first meta-analyses in 2016 reviewed medicinal plants used in traditional Persian medicine to treat spermatogenesis-related disorders (data collected for the period from 1966 to March 2015) (Tahvilzadeh et al. 2016). Some plants, such as *Chlorophytum borivilianum*, *Crocus sativus*, *Nigella sativa*, *Sesamum indicum*, *Tribulus terrestris*, *Mucuna pruriens*, and *Withania somnifera*, have been shown to be the most effective in treating male infertility. Apparently, their beneficial effects are associated with saponins, phytosterols, carotenoids, polyphenols and alkaloids in their composition (Tahvilzadeh et al. 2016). The beneficial effect of medicinal plants on sperm abnormalities is due to their antioxidant, anti–inflammatory, decongestant and venotonic activity, as well as the presence of phytoprecursors of ejaculate components and precursors of testosterone synthesis in the composition of these plants (Tahvilzadeh et al. 2016).

The systematic review of 2021 summarizes the results of available studies to determine the efficacy, safety, and mechanism of action of medicinal herbs to improve male fertility. The Medline/PubMed, Scopus, Science Direct, and Cochrane Central Register of Controlled Trials (Central) databases were searched for randomized controlled trials (RCTs) that were published between 2000 and 2020 (Roozbeh et al. 2021). The review includes 20 RCTs that meet the inclusion criteria with 1,519 participants overall. These studies compared the effects of various medicinal plants and their complexes (*Ginseng, Saffron, Nigella sativa, Palmpollen, Sesame, Mucuna pruriens* and the TOPALAF complex (a complex of *Tribulus terrestris, Orchis mascula, Phoenix dactylifera, Allium ampeloprasum, Lepidium sativus, Amygdalus communis* and *Ficus carica*)). All studies (except one) have demonstrated the beneficial effects of these medicinal plants on male reproduction; however, more clinical trials are required to establish the maximum dose and treatment duration with herbal medicines, as well as to evaluate any possible adverse effects of this therapy, in order to develop novel strategies for the treatment of male infertility (Roozbeh et al. 2021). The authors of the new systematic review of 2022 searched the databases Science Direct, PubMed, Scopus, PubMed Central, and Scientific between 2000 and 2020 using search queries (Boroujeni et al. 2022). Based on the results of 35 studies, it was determined that such plants as *Apium graveolens, Cinnamomum camphora, Cornus mas, Satureja khuzestanica, Withania somnifera, Fumaria parviflora, Zingiber officinale, Cinnamomum zeylanicum* and *Phoenix dactylifera* had a positive effect on reproduction, and demonstrated antioxidant effects and a low frequency of side effects (Boroujeni et al. 2022). Many nutraceuticals can stimulate steroidogenesis in men, according to Santos et al. (2022). However, only a small number of these products (zinc, vitamin D (in the case of hypovitaminosis D), L-arginine, *Mucuna pruriens*, and *Withania somnifera*) demonstrate promising results based on the results of high-quality randomized controlled trials (Santos et al. 2022). These same natural substances, along with *Tribulus terrestris* and ω-3 polyunsaturated fatty acids, can somewhat improve the parameters of the ejaculate in infertile men, with the exception of L-arginine (Santos et al. 2022). Ahmadian et al. (2022) performed a systematic review in order to assess the most recent scientific data on herbal substances used for the treatment of idiopathic male infertility (Ahmadian et al. 2022). They searched online literary sources up to 2020 in only English and Persian using various search systems (ISI, Web of Knowledge, Medline, PubMed, Scopus and Google Scholar). Consequently, 14 RCTs involving 1,218 men were included in the systematic review out of the 851 identified articles. Twelve of the fifteen plants and phytopharmaceutical

drugs identified in the chosen studies were effective in the treatment of idiopathic male infertility (*Whitania somnifera, Alpinia officinarum, Nigella sativa, Lycopersicum, Ceratonia siliqua*, as well as combination herbal medicinal products marketed as Xperm, PHF, ChurnaRatnam, SvaguptadiChurna, Y virgin capsules, Manix capsules, and Tradafertiltablets). Each of these plants or products influenced certain components of male fertility mainly due to their antioxidant effects without any serious side effects (Ahmadian et al. 2022). In the most recent systematic review published by Shepherd et al. (2022), the authors critically evaluated the related RCTs published over the previous five years and compared the main clinical data on the various effects of plant components on the testicles (Shepherd et al. 2022). The researches collected and analyzed systematic reviews, meta-analyses, and RCT reports on the impact of plants on male fertility and testicular function from the PubMed, Web of Science, Scopus, Embase, ProQuest, Cochrane Library, and Google Scholar databases between their creation and May 10, 2022.RCTs published since 2018 have been critically evaluated in accordance with the good clinical practice for RCTs and herb research reporting. The authors found 24 systematic reviews and meta–analyses published since 2005 by scientists from Iran (25%), China (21%), the USA (12.5%) and 9 – from other countries. All but two were published in English. Only three systematic review protocols were found, and they were all published in China during the previous three years in English. A total of 125 RCTs were found in six languages, mainly in Chinese (42%), and English (55%). Since 1994, they have been published in 23 countries across all six inhabited continents. China has contributed the most, with 46% of the papers, followed by Australia (8%), the USA (8%), India (7%), and Iran (5%). RCTs published in English were about efficacy (herbal drugs versus placebo) and comparative efficacy (herbal drugs versus other treatments) in 72% and 28%, respectively. On the other hand, only 2% of RCT reports in Chinese discussed efficiency, and 98% of them focused on comparative effectiveness. Of the 125 RCTs, 57% were conducted on patients with male infertility and/or sperm abnormalities, 22% investigated the impact of herbs on healthy men, 14% involved patients with hypogonadism and male sexual dysfunction, and 7% involved men with non-sexual disorders. Since 2018, 32 RCTs have been published in English (69%) or Chinese (31%). Thirteen RCT reports from Australia, Brazil, the Czech Republic and Italy, Iran, Malaysia, Spain, the UK and the USA examined extracts of a single species, whereas nineteen RCT reports from China, India, Japan, and Korea examined herbal forms.The study revealed that gossypol and *Tripterygium wilfordii* extracts have adverse effects on male fertility and testicles. In contrast, *Withania somnifera* extracts and the Qilin Wan complex of traditional Chinese medicine (which included *Lycium chinense, Rubus idaeus, Schizandra chinensis, Plantago asiatica*, and *Cuscuta*) were able to increase testosterone levels and improve spermogram parameters, making them potentially effective therapeutic options for male sexual dysfunction and infertility. However, all of them still require further evaluation because there have been persistent issues with plant material quality control, design development, and RCT reporting.

Research on the impact of plant components on male reproductive function has been published all over the world. These studies demonstrate significant geocultural differences in the plant species, botanical types, and research objectives that are studied, as well as in the quality of research development, performance, and reporting. For this reason, the use of any particular herbal component to increase male fertility cannot be clearly recommended by this review; however, available data suggest that herbal components may have opposing effects on testicles and male fertility (Shepherd et al. 2022).

Conclusion

The issue of effective treatment of male infertility is still very important for a variety of reasons. It should be noted that in the vast majority of cases, specific mechanisms of reproductive disorders in a man remain unknown even after his comprehensive examination by a team of specialists in reproductive medicine. In this case, it is necessary to prescribe not pathogenetic, but empirical therapy, including elements of phytotherapy, the effectiveness of which remains unpredictable and rather low.It should be understood that the combination of pathogenetic therapy with empirical phytotherapy for identified male infertility (for example, stimulation with chorionic gonadotropin+phytotherapy or varicocele surgery+phytotherapy) is one side of the coin. A different matter is men with idiopathic infertility, who want to conceive through a natural cycle. In this case, empirical phytotherapy is a kind of "last-resort treatable" before the use of ART methods, for which not all couples are immediately ready. Thus, it is clear that phytotherapy can be applied within a rational framework that acknowledges its generally low efficacy without unnecessarily extending the course of treatment. Data from the literature suggest that not all plant substances with a "reproductive effect" positioned in them actually have such proven effects. Consequently, the selection of phytotherapeutic agents in the management of idiopathic male infertility must be done with great caution, particularly when choosing phytotherapy as an empirical monotherapy for male reproductive disorders.

Conflict of interests

The authors declare no conflict of interests.

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