

A Systematic Review on Use of Medicinal Plants for Male Infertility Treatment

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Abstract

Objective: Male infertility is involved in about half of the cases of infertility and the only sole reason for infertility in 20%-30% of the cases. Following the recent interest in the use of medicinal plants, scientists have sought to clarify their effects on male fertility. This review aimed to summarize the results of studies available to determine the effectiveness, safety and mechanism of herbal treatments in the improvement of male fertility.

Materials and methods: Medline/PubMed, Scopus, Science Direct, and the Cochrane Central Register of Controlled Trials (Central) databases were searched for randomized controlled trials (RCTs) published during 2000-2020. Studies were only included if they adhered to the CONSORT checklist. The methodological quality of the selected studies was assessed using the Cochrane risk of bias tool.

Results: Finally, 20 studies recruiting a total of 1519 individuals were reviewed. These studies compared the effects of eleven different medicinal plants, i.e. ginseng, saffron, *Nigella sativa*, palm pollen, ADOFON, TOPALAF, sesame, and *Mucuna pruriens*, on male fertility with those of placebo. All studies (except one) confirmed the beneficial effects of medicinal plants on the improvement of sperm and reproductive parameters and thus male infertility.

Conclusion: The existing RCTs indicated the positive effects of medicinal plants on male fertility. Therefore, in order to develop a novel approach to the treatment of male infertility, further clinical trials are warranted to determine the maximum dosage and duration of treatment with herbal medicines and evaluate any potential side effects of such interventions.

Keywords: Male Infertility; Medicinal Plants; Fertility

Introduction

With a prevalence rate of 2.5%-12%, male infertility

affects over 30 million men around the world. It is the sole reason and the contributing factor for 20%-30% and half of all cases of infertility, respectively (1, 2). Since male fertility largely depends on sperm count, quality, motility, and morphology, defects in any of these factors can lead to infertility (3). A large

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percentage (up to 90%) of all infertile couples have to deal with low sperm count and/or quality (4). Under development of the testicles, reproductive system diseases, elevated scrotal temperature, immune system and endocrine disorders, and lifestyle, along with environmental and nutritional factors have been reported to negatively affect sperm parameters and cause male infertility (5).

Complementary therapies for infertility have received growing attention during recent years and various antioxidants, nutritional approaches, and medicinal plants have been proposed for the treatment of fertility problems in infertile and sub fertile couples (6). Several medicinal plants with antifertility or fertility boosting effects have been traditionally used to either decrease or increase male fertility throughout the world. Fertility-related properties of these plants have also been the subject of interest in modern scientific research (7). Following men's increasing interest in effective herbal treatments of infertility, complementary approaches to infertility treatment have received growing attention (8). The European Association of Urology has recently reported the use of complementary treatments based on traditional medicine as a multidimensional integrative approach to male infertility treatment (9). The World Health Organization (WHO) encourages the use of medicinal plants, and suggested researchers to define the rational use of medicinal plants as a source of new treatments (10). Such a growing interest in medicinal plants has inspired scientists to clarify their effects on male fertility. Based on the available literature, some of these plants increase sperm count and motility while a number of others alter the secretion of hormones by the testicles (11). The flavonoids and phenolic compounds in some plants serve as potent antioxidants against oxygenated free radicals. They actually protect the sperms against free radicals and improve sperm quality and fertility parameters (12). However, according to the World Health Organization (WHO), despite the wide use of herbal medicines, scientific knowledge on their properties is still scarce. It is hence essential to evaluate the effects of biologically active herbal compounds on male fertility and to identify natural compounds with estrogenic and anti-estrogenic properties(5). Therefore, this review aimed to summarize the results of studies available to determining the effectiveness, safety and mechanism of herbal treatments in the improvement of male fertility.

Materials and methods

Search strategy: Medline/PubMed, Scopus, Science Direct, and the Cochrane Central Register of Controlled Trials (Central) databases were searched for English articles published during 2000-2017 which contained a number of key terms including "male fertility", "medicinal plants", and "male infertility". The keywords in each group were combined using the Boolean operator "OR". All searches containing at least one keyword from each group were combined using the Boolean operator "AND". The search process was completed in September 2020.

Inclusion and exclusion criteria: This review only included randomized controlled trials (RCTs) evaluating the effects of medicinal plants (irrespective of treatment duration and route of administration) on improving sperm parameters, testicular function, and male reproductive system disorders and comparing these effects with those of no treatment, treatment with placebo, and treatment with other non-herbal agents. Studies without a control group and those without numerical outcome data were excluded. Observational and qualitative studies, case reports, and papers presenting a subgroup analysis of another primary study were also excluded. No language limitations were imposed during the search process.

Study selection: Two authors (FA and NR) evaluated the titles and abstracts of the search results, retrieved the full texts of potentially relevant RCTs, and examined the eligibility of the extracted articles. Studies were only included if they contained all the required information based on the 25-item Consolidated Standards of Reporting Trials (CONSORT) checklist (13). Cases of disagreement about article eligibility were resolved through consensus.

Data extraction: The same two authors independently extracted and recorded study characteristics including the name of the administered medicinal plant, the participants and their grouping, the interventions and their duration, measured outcomes, and effectiveness parameters. The extracted data were then compared and cases of disagreement were resolved through consensus.

Risk of bias assessment in the selected studies: The mentioned authors used the Cochrane Risk of Bias Assessment Tool (14) to independently assess the risk of bias by evaluating the randomization method, allocation concealment, blinding processes, incomplete outcome data, and selective outcome reporting (Table 1). Then the results were compared and cases of disagreement were resolved through consensus.

Table 1: Summarized results of the studies

Authors (years)	Plant name	Participants	Intervention (daily dose)	Control group	Duration	Study outcome measures	Improvements	Side effect	Consort score
Heidary (2008), (15)	Saffron	52 nonsmoker infertile men	50mg	Placebo	3 months	Semen parameters	Sperm morphology and motility(p<0.001)	None reported	16
Safarinejad (2011), (16)	Saffron	260 infertile men	60 mg	Placebo	26 weeks	Semen parameters and total seminal plasma antioxidant capacity	No improvement	Safe	19
Shamsa (2009), (17)	Saffron	20 male patients with ED	200mg	Placebo	10 days	RigiScan parameters and sexual function	Rigidity, tumescence, erectile function, sexual satisfaction, orgasm, sexual desire and overall satisfaction (p<0.001)	None reported	20
Rasekh (2015), (18)	Palm pollen	50 infertile men	120 mg/ kg	Placebo	2 months	Sperm parameters	Sperm motility, morphology and forward progressive motility (p<0.05)	None reported	17
Saeed (2020), (19)	Date Palm pollen	40 subfertile men	500mg	Control	3months	Semen parameters and serum hormone levels	sperm motility in oligoasthenozoospermic patients (p<0.05)	Safe	17
Khoradmehr (2015), (20)	TOPALAF	62 infertile men	12.5 mg	Placebo	3months	Sperm parameters	Count and sperm motility(p<0.05)	None reported	16
Ramezani (2015), (21)	ADOFON	62 infertile men	12.5 mg	Placebo	3months	Sperm parameters	Count and sperm motility(p<0.05)	None reported	16
Kim (2002), (22)	Ginseng	80 patients with abnormal semen	2.4 gm	Placebo	2 months	Sperm parameters	Count and Semen volume (p<0.05)	None reported	17
Park (2016), (23)	Ginseng	80infertile men	1.5-g	Placebo	3 months	Sperm analysis was performed and hormonal levels	Sperm concentrations, motility, morphology, and viability(p<0.05)	None reported	21
Khani (2013), (24)	Sesame	25 infertile men	0.5 mg/kg	Placebo	3months	Sperm parameters	Sperm count and motility(p<0.05)	No major side effect was reported.	18
Kolahdooz (2014), (25)	Nigella sativa	34 Iranian infertile men	5 ml	Placebo	2 months	Sperm parameters	Sperm count, motility and morphology and semen volume, pH and round cells (p<0.05)	Safe	22
Marbat (2013), (26)	Nigella sativa	50 infertile men	2g	Placebo	3 months	Sperm analysis was performed and hormonal levels	Sperm count, motility, viability, morphology, serum FSH, LH and testosterone levels (p<0.01)	None reported	15
Ambiye (2013), (27)	Ashwagandha	68infertile men	675 mg	Placebo	3 months	Semen parameters and serum hormone levels	Sperm count, volume, motility, testosterone and LH levels (p<0.05)	Safe	20

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Table 1: Summarized results of the studies (continue)

Authors (years)	Plant name	Participants	Intervention (daily dose)	Control group	Duration	Study outcome measures	Improvements	Side effect	Consort score
Ahmad (2010), (28)	Ashwagandha	75 normal healthy fertile men	5 g	Placebo	3 months	Seminal plasma biochemical parameters, antioxidant vitamins, and hormone levels	Sperm count, motility, seminal plasma levels of antioxidant enzymes, vitamins A, C, and E, testosterone and LH levels (p<0.05)	Safe	17
Mahdi (2011), (29)	Ashwagandha	121 infertile men	5 g	Placebo	3 months	Seminal plasma biochemical parameters, antioxidant vitamins, and hormone levels	Sperm count, motility, seminal plasma levels of antioxidant enzymes, testosterone and LH levels (p<0.05)	None reported	17
Mares (2012), (30)	Ashwagandha	75 infertile men	No reported	Placebo	3 months	Semen parameters and serum hormone levels	Sperm count, motility, viability, morphology, volume, serum glutathione, serum FSH, LH and testosterone levels(p<0.05)	None reported	15
Gupta (2013), (31)	Ashwagandha	180 infertile men	5 g	Placebo	3 months	Semen parameters and serum hormone levels	Sperm count, motility, disturbed concentrations of lactate, alanine, citrate, GPC, histidine, and phenylalanine in seminal plasma (p<0.05)	None reported	18
Shukla (2009), (32)	Mucunapuriens	75 infertile men	5 g	Placebo	3 months	Semen parameters and serum hormone levels	Sperm count and motility, and LH, dopamine, adrenaline, and noradrenaline levels(p<0.05)	None reported	18
Mkrtchyan (2005), (33)	<i>Andrographis paniculata</i>	50 infertile men	60 mg	ginseng	13 days	Semen parameters	Sperm volume, and count (p<0.05)	Safe	17
Kolangi (2019), (34)	<i>Alpinia officinarum</i>	60 infertile men	300 mg	Placebo	3 months	Sperm parameters	Sperm count and morphology(p<0.05)	Safe	22

Results

After the primary search, the information provided in 167 papers was individually assessed. Duplicate articles were then excluded and the abstracts and titles of the remaining 126 papers were reviewed. In the next stage, 94 unrelated papers were excluded. Five papers that lacked specific data were also excluded. Evaluating the full texts of the remaining articles confirmed the eligibility of only 20 papers. Figure 1 shows the flow diagram of the literature review process. Afterward, the main findings of the selected papers were summarized and the articles were scored based on their adherence to CONSORT checklist (Table 2). The studies were then evaluated in terms of bias (Table 1). The selected studies were performed on 20-260 participants and a total of 1519 individuals were included in the 20 eligible studies. The selected RCTs were placebo, ginseng and pretest controlled. They implemented a variety of interventions and used various medicinal plants including ashwagandha (n = 5), ginseng (n = 2), saffron (n = 3), Nigella sativa (n = 2), palm pollen (n = 2), ADOFON (n = 1), TOPALAF (n = 1), sesame (n = 1), Andrographis paniculata (n = 1), Alpinia officinarum (n = 1) and Mucuna pruriens (n = 1).

The interventions lasted for 10 days to 26 weeks

(three months in 14 studies). In most selected papers, the main measured outcome was the effectiveness of the intervention which was determined in terms of sperm and semen parameters, serum hormone levels, total seminal plasma antioxidant capacity, RigiScan parameters, sexual function, seminal plasma biochemical parameters, and antioxidant vitamins.

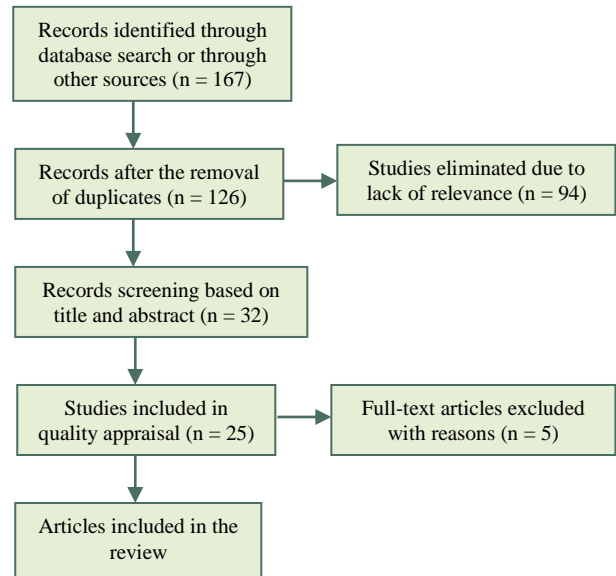


Figure 1: Flow diagram of the search process

Table 2: Risk of bias summary (Authors' judgments of each risk of bias item for each included study)

		Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
1	Heidary et al. (2008)	?	-	?	+	?
2	Safarinejad et al. (2011)	?	?	+	+	+
3	Shamsaa et al. (2009)	-	?	?	+	?
4	Rasekh et al. (2015)	?	?	+	+	?
5	Saeed et al. (2020)	+	?	?	+	+
6	Kharadmehr et al. (2015)	-	-	?	?	+
7	Ramezani et al. (2015)	-	-	?	?	+
8	Kim YT et al. (2002)	?	?	?	+	+
9	Park et al. (2016)	+	?	+	+	?
10	Khani et al. (2013)	?	?	?	+	+
11	Kolahdooz et al. (2014)	+	?	+	+	?
12	Mossa et al. (2013)	-	-	?	?	?
13	Ambiyeet al. (2013)	+	?	+	+	+
14	Kaleem Ahmad et al. (2009)	?	?	?	+	?
15	Mahdi et al. (2011)	+	?	?	+	?
16	Mares et al. (2012)	-	-	?	?	?
17	Gupta et al. (2013)	?	?	+	+	?
18	Shukla et al. (2009)	- ?	?	?	+	?
19	Mkrtchyan et al.(2005)		?	?	-	-
20	Kolangi et al. (2019)	+	+	+	?	?

Green= Low risk of bias; Red= High risk of bias; Yellow= Unknown risk of bias

All studies (except one) confirmed the beneficial effects of the administered plants on male infertility, sperm parameters and sexual function. The majority of the selected papers did not find any adverse effects following the use of medicinal plants. Moreover, 8 studies directly reported the safety of the plants. Most studies (n = 15) highlighted improved sperm parameters, specifically sperm count and motility, after the interventions. Also in one study, intervention affected sexual function among participation.

We assessed bias in all studies by using the Cochrane tool. Attrition bias was rated low in all studies (72%). None of the studies had a high risk of detection bias. There was an unknown risk in performance bias (72%) in most studies. Across studies, the risk of bias was generally unknown.

Discussion

Due to the significance of male infertility, this systematic review summarized the results of 20 high-quality studies with a low risk of bias to clarify the effects of medicinal plants on male fertility. Based on the reviewed RCTs, medicinal plants improved semen volume and sperm quality in infertile men.

Efforts to identify the possible mode of action of herbs against infertility showed that the use of these natural products by infertile men significantly regulated not only the levels of male sex hormones but also sperm motility and concentration. While the reviewed studies generally confirmed the efficacy of medicinal plants in promoting male fertility, they were not always in agreement in cases of effectiveness and side effects.

Differences in the daily dose of the medical plants might have been responsible for such controversies. In other words, the effects of medicinal plants on male fertility were determined by type of plant and content, the use dosage, and the duration of the interventions.

Several potential approaches for infertility have been investigated over a long time including genetic, hormonal, chemical and immunological approaches. According to some studies, oligosaccharides, i.e. active constituents of medicinal plants with fertility-boosting effects, were able to protect the DNA of human sperm against damage (35). The results of the present study showed medicinal plants modulate estrogen, progesterone, FSH, LH, and GnRH levels.

Shukla et al. showed that the administration of *M. pruriens* in infertile men significantly increased testosterone, luteinizing hormone (LH), dopamine, adrenaline, and noradrenaline levels but decreased follicle-stimulating hormone (FSH) and prolactin

levels. Moreover, the treatment restored sperm count and motility to their normal ranges (32).

Another research highlighted the potential role of micro-elements isolated from palm pollen, e.g. estrogen and sterols, in enhancing male fertility and improving sperm motility and viability, acrosome reaction, and lipid peroxidation (36). Moreover, by boosting the immune system, saffron not only reduces oxidative stresses, but also increases the lifespan of spermatozoa and the number of viable spermatozoa (37). The compounds in saffron stimulate FSH, LH, and testosterone hormones and thus promote epithelial cell proliferation in seminiferous tubules, enhance the activity of Leydig cells, increase the number of spermatocytes, and ultimately promote spermatogenesis (38).

According to previous research, some medicinal plants prevent free radicals, lipid peroxidation, and sperm damage by improving antioxidant activity. They also increase the number of testicular veins, the number and lifespan of spermatozoa, protect germ cells, and enhance the activity of the hypothalamic-pituitary-gonadal axis (4).

Many studies on the use of medicinal plants for the treatment of male infertility have focused on *Withania somnifera*. Treatment with *W. somnifera* was found to restore LH, FSH, and prolactin levels which are directly correlated with semen quality. Furthermore, the aqueous extract of this plant promoted gonadotropin secretion, improved epididymis sperm pattern, and stimulated testicular development and spermatogenesis through its direct effects on seminiferous tubules (28). Owing to the alkaloids, ergostane steroids, amino acids (including tryptophan), central nervous system inhibitors, centrally acting hypotensive agents, and gamma-aminobutyric acid (GABA) and serotonin agonists available in its roots, *W. somnifera* can treat stress-induced infertility (29). As reported by two clinical trials and several animal studies, ginseng enhanced spermatogenesis by promoting the expression of glial cell-derived neurotrophic factor (GDNF). GDNF is a growth factor involved in the communication between sertoli cells and spermatogonia. Ginseng can also upregulate C21-steroid hormone metabolism via Cyp11a1 and thus cause anti-aging effects in senescent rat testes (23). The beneficial effects of *Nigella sativa* on sperm and reproductive parameters have also been documented in various studies. This study showed many beneficial effects of medicinal plants on male infertility treatment are associated with antioxidant

effects. This suggests that antioxidants have been to improve spermatogenesis of male reproduction system.

Although the exact mechanisms of these effects are still unknown, the antioxidant properties of *N. sativa* have been suggested to be responsible. While the antioxidants in semen can normally neutralize reactive oxygen species (ROS), decreased antioxidant property or increased ROS content of the semen would elevate the oxidative stress levels and damage sperm parameters (39).

Despite the existing controversies over the exact effects of medicinal plants on male infertility, in vitro and animal studies have confirmed the benefits of a number of herbal medicines in promoting men fertility. These benefits have been justified by the effects of medicinal plants on both the central nervous system and the reproductive tract. Nevertheless, further in-depth studies are required to elucidate such effects.

Conclusion

In conclusion, previous RCTs have highlighted the fertility-boosting effects of medicinal plants in men. However, in order to develop a new approach toward the treatment of male fertility, further RCTs are warranted to confirm the mentioned effects, determine the maximum dosage and duration of treatment with herbal medicines, and evaluate any potential side effects of such treatments. Like any other study, this review had a number of limitations. First, some of the selected studies had low methodological quality and very small sample size. Furthermore, articles in languages other than English were not included. Lack of information about the use of novel herbal therapies in men's infertility was another limitation of our review.

Conflict of Interests

Authors have no conflict of interests.

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