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INTERVENTION OF MEDICINAL PLANTS FOR IMPROVING MALE FERTILITY

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ABSTRACT

Sexuality is a complex interplay of multiple facets, including anatomical, physiological, psychological, developmental, cultural, and relational factors. This complex process might be divided into four phases, namely desire, arousal, orgasm, and resolution. Male infertility is a major problem worldwide which is defined as the inability of sexually active, non-contraceptive couples to have offspring in a year. Many factors affect the quality of semen including environmental, nutritional, and "lifestyle-related reasons. Male infertility problems may be contributory to 30 to 40 percent of infertile couples. There are many qualitative and quantitative parameters to check infertility in men which are quality of semen, number of sperm per ml of semen, sperm motility, abnormalities in sperm morphology, etc. Many plants are scientifically studied for their effect on male sexual dysfunction. Evidence showed that plants investigated on male infertility uplift the level of testosterone. The studies made it clear that testosterone plays an important role in sexual interest and associated sexual arousal.

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Introduction

The inability of a sexually active, non-contraceptive couple to become pregnant within a year is known as infertility [1]. According to a review by Agrawal *et al*., the percentage of infertile men ranged from 2.5% to 12%, and the distribution of infertility caused by male factors ranged from 20% to 70%. The highest rates of infertility were found in Central/Eastern Europe and Africa [2].

A problem with the seminal fluid or the quantity and morphology of sperm could be the cause of male infertility. Men are deemed infertile when their sperm concentration falls below 20 million/mL [3]. According to WHO reports, there are 60-80 million infertile couples worldwide [1].

Around the world, 8–12% of couples experience infertility, with regional differences [4]. About 10% of American couples are classified as infertile if they are unable to conceive after 12 months of unprotected sexual activity [5, 6]. According to the National Center for Health Statistics, the total number of women with impaired fecundity increased by about 2.7 million between 1982 and 2002, from 4.56 million to 7.26 million, before slightly declining to 6.71 million between 2006 and 2010 [7]. In 2015, there were 22.3 teenagers born per 1,000 females, an 8% decrease from the previous year [8]. Prevalene of male sexual dysfunction in Asia is shown in **Table 1**.

The persistent inability to obtain and maintain an erection strong enough to allow for satisfactory sexual performance is known as erectile dysfunction (ED) [9]. Premature ejaculation is a male sexual dysfunction that is characterized by ejaculation that always, or nearly always, occurs before or within a minute of vaginal penetration, according to the International Society of Sexual Medicine [10]. As a clinical and biochemical syndrome associated with getting older and characterized by sexual dysfunction and other typical symptoms as well as a lack of serum testosterone levels, hypogonadism is the clinical and biochemical entity formerly known as andropause, androgen deficiency in the aging male, and partial androgen deficiency in the aging male [11].

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Table 1. Prevalence of male sexual dysfunction in Asia [12]

	Prevalence (%)		
Country	**Erectile dysfunction**	**Premature ejaculation**	**Hypogonadism**
Malaysia	26.8-69	22.3	18.5
Mainland China	38.3	19.5	-
Korea	32.2	27.5	-
Taiwan, China	9-17.7	13	24.1
Thailand	37.5	23	-
Singapore	51.3-73	12	-
Hong Kong, China	63.6	29.7	9.52

Although there are many treatments available, including phosphodiesterase type 5 inhibitors, intracavernosal prostaglandin E1, medicated urethral systems for erection, vacuum devices, and penile prostheses for erectile dysfunction; testosterone replacement therapy for hypogonadism; psychological and behavioral therapy, local anesthetic creams, tramadol, and selective serotonin reuptake inhibitors are used for premature ejaculation [12]. The use of numerous plants and Ayurvedic formulas as aphrodisiacs is documented in ancient literature.

Meiosis, spermatogenesis, and mitotic cell division all play a part in the intricate process known as spermatogenesis. Both endocrine and paracrine mechanisms are involved in regulating spermatogenesis. Follicle stimulating hormone (FSH) and luteinizing hormone (LH), the latter acting through the intermediary of testosterone, which is produced by the Leydig cells in the testis, are both involved in the endocrine stimulation of spermatogenesis [13].

The keywords, male infertility, clinical evaluation, and medicinal plants were searched on PubMed, MEDLINE, EBSCO, and Google Scholar. Around 250 articles were reviewed on the effect of medicinal plants on male infertility. Those articles which showed no or less effect of medicinal plants on infertility were excluded. Preclinical and clinical studies on effects of plants on male infertility are mentioned in **Table 2** and **Table 3** respectively.

Table 2. Preclinical studies on effects of medicinal plants on male infertility

Name of the plant	**Part of the plant**	**Animal/ Cell used**	**Dose level**	**Efficacy**	**Mechanism**	**Ref**
Pedalium murex	Ethanolic extract of the fruits	Albino rats	50,100 and 150 mg/kg	Increased and improved sexual performance, increased levels of serum testosterone	Nitric oxide release	[14]
Pedalium murex	Petroleum ether extract of a plant	Albino rats	200 and 400 mg/kg	Higher increment of mating performance, increased pregnancy rate, increased levels of testosterone by antioxidants	Viable sperm of the male rats, protection of germ and Sertoli cells	[15]
Citrullus lanatus	Methanolic extract of the rind of the fruit	Albino rats	200 mg/kg	Improvement in all the semen parameters, sperm count; increase in FSH, LH, and testosterone	High phenolic flavonoid and ascorbic acid contents act as anti-oxidants; ascorbic acid enhances testosterone synthesis and release of FSH and LH	[16]
Amaranthus spinosus	Methanolic extract of stem	Albino rats	250 and 500 mg/kg	Increase in the sperm count, increase in serum and testicular testosterone; the weight of testis,	-	[17]
Dactylorhiza hatagirea	Lyophilized aqueous extract of roots	Albino rats	200 mg/kg	Increased sexual behavior, penile erection index	Involvement of nitrous oxide (NO)	[18]

Lecaniodiscus cupanioides	Aqueous extract of roots	Wistar	25, 50, and 100 mg/kg	Increased sexual behavior, increased levels of testosterone, LH, FSH	Reduce the synaptic concentration of serotonin as well as increase the amount of dopamine release	[19]
Fadogia agrestis	Aqueous extract of stem	Albino rats	18, 50 and 100 mg/kg	Increased sexual behavior, testosterone,	Because it increases androgen, saponin, a plant component, enhances the aphrodisiac effects.	[20]
Piper guineense	Aqueous extract of dry fruits	Sprague Dawley	200 mg/kg	Increase in testicular weight, testosterone; normal parameter of semen analysis	Zinc is a co- essential factor for the endogenous production of testosterone by inhibiting the conversion of testosterone to dihydrotestosterone	[21]
Garcinia kola	Ethanolic extract of seeds	Wistar rats	200 and 400 mg/kg	Increased pre-coital sexual behavior; increase in weight of testis, testosterone,	factors that increase gonadotropins or locally through an increase in Leydig cells' number or their sensitivity to LH	[22]
Fumaria parviflora	Ethanolic extract of leaves	Wistar rats	100, 200 and 400 mg/kg	Increases in the testis and epididymis weight; seminiferous tubules diameter and germinal epithelium height were higher; increase in sperm density; No significant differences in serum FSH and LH; increase in testosterone	Increased androgen biosynthesis, improvement of testicular oxidative status by its extract components	[23]
Nigella sativa	Ethanolic extract of seeds	Wistar rats	200 and 400 mg/kg	No effect on the sperm motility and viability; increase in sperm count, testosterone, LH, fertility index	Increase in LH hormone concentration; LH stimulates the production of testosterone in Leydig cells, which stimulates spermatogenesis via testosterone, Thymoquinone	[24]
	Seed oil	Rabbits	5 ml/kg	The higher number of spermatozoa, an increase in testosterone,	Thymoquinone as antioxidant	[25]
Cardiospermum halicacabum L	Aqueous extract of leaves	Wistar rats	100 and 200 mg/kg	No significant change in reproductive organ weight; a significant increase in total sperm count, motile sperm, testosterone	An increase in serum testosterone levels, antioxidant activity brought on by flavonoids, and an increase in plasma levels of testosterone that may be caused by plant saponin components	[26]
Basella alba	Methanolic extract of leaves	Leydig cells	10 and 100 µg/ml	Stimulates testosterone, estradiol, mRNA levels of aromatase,	Regulation of protein kinases and cAMP	[27]
Basella alba and Hibiscus macranthus Hochst A ex Rich	Aqueous extract of both fresh and dried leaves	Albino rats	720 mg/kg (Fresh leaves extract), 108 mg/kg (Dry leaves extract)	An abundance of spermatozoa in the seminiferous tubule, an increase in testosterone level,	Induction of synthesis of testosterone by the Leydig cells	[28]
Carpolobia alba	Aqueous extract of roots	Sprague-Dawley	0.001, 0.01, 0.1, 1 and 10 mg/kg	Increase the level of testosterone *in vivo* and in *vitro*	-	[29]

Anacyclus pyrethrum	Alcoholic extract of roots	Albino rats	50,100 and 150 mg/kg	Increase sperm count, motility, serum FSH, LH, and testosterone	Stimulation of the hypothalamus-adenohypophysis- gonad axis	[30]
Jurenia dolomiaea	Methanolic extract of the root	Sprague–Dawley	200 and 400 mg/kg	Increase the level of testosterone; density of germinal cells and sperms in the seminiferous tubules	Pituitary LH release may be caused by saponins, whereas the synthesis of androgens may be mediated by flavonoids.	[31]
Urtica dioica	Hydro-alcoholic extract of leaves	BALB/c male mice	10, 20, and 50 mg/kg	Increase in weight of testis, sperm motility, sperm count, testosterone; normal sperm morphology	Enhancing the anti-oxidant defense, inhibition of cannabinoids' activity	[32]
Allium sativum	Aqueous extracts of bulb	Sprague-Dawley	200 mg/kg	Increase in testicular weight, Serum testosterone	According to reports, selenium and zinc regulate testicular activities, particularly the production of steroidogenic enzymes.	[33]
Eruca sativa	Aqueous extract of leaves	Albino mice	30 and 40 mg/kg	Increase in testosterone, a significant decrease in sperm mortality and abnormalities, a significant increase in diameter of seminiferous tubules and spermatid	Encourage the development of the testes and improve spermatozoa proliferation, maturation, and differentiation	[34]
Ashwagandhadi Lehya (Withania somnifera)	Ayurvedic formulation *Ashwagandhadi lehya*	Wistar rats	250, 500, 750 mg/kg *Ashwagandhadi Lehya*, 250 mg/kg *Withania somnifera*	The increased serum concentration of testosterone and cholesterol; spermatozoa, the diameter of seminiferous tubules	Nitric oxide synthesis	[35]
Hygrophila spinosa T. Ander	Unsaponifiable fraction of seeds	Wistar rats	100, 200 and 300 mg/kg	Increased concentration of testosterone, sperm counts; increased diameter of seminiferous tubules, high numbers of spermatozoa in seminiferous tubules	Through interaction with Leydig cells, a fraction could elevate serum testosterone levels in animals receiving treatment.	[36]
Argyreia speciosa	Alkaloidal fraction of root	Leydig cell	10, 100, and 1000 µg/ml	Increased concentration of testosterone.	Synthesis of testosterone.	[37]
Phyllanthus amarus	Methanolic extracts from the leaves	Guinea pigs	100, 200, 400 and 800 mg/kg	Increases in the level of testosterone but has little or no effect on the levels of FSH and LH	Increase in the level of testosterone can lead to an increase in the spermatozoa	[38]
	Aqueous and methanolic extract of leaves and stem	Albino rats	200 and 400 mg/kg	An increase in Testosterone levels increased Sperm concentration	Stimulation of the sex organs	[39]

Table 3. Clinical studies on medicinal plants which improve fertility

Plant' s name	**Patients & methods**	**Period of treatment**	**Efficacy**	**Findings**	**Ref**
Zingiber officinale	75 infertile men	3 months	Increase in sperm count, sperm motility, sperm viability, normal sperm morphology; increase in ejaculate volume; increases in serum FSH, LH & testosterone	Increase the α-glycosidase enzyme in the epididymis, and fructose sugar in seminal vesicle	[40]

Mucuna pruriens	150 men	3 months	Infertile men's levels of testosterone, LH, dopamine, adrenaline, and noradrenaline significantly improved	Dopamine-mediated CNS action and adrenaline- and noradrenaline-mediated action on the reproductive tract	[41]
Withania somnifera	75	3 months	increased serum levels of testosterone and LH, decreased levels of FSH and prolactin, and improved sperm motility and count.	Choline, beta-sitosterol, withanolides I–VII, withaferin A, and sitoindo-sides VII–X may all play a role in the various effects of W. somnifera on semen properties.	[42]
	46(n=21)	90 days	Increase in sperm count, semen volume, motility; increase in serum testosterone, LH	Higher levels of testosterone;	[43]
	50	90 days	Increase in serum testosterone, sperm concentration, % motile sperm	Improved serum testosterone; testicular synthesis of peptides, which had effects on sperm motility	[44]
Nigella sativa L.	80(n=40)	2 months	Significant improvement in sperm count, motility and morphology and semen volume, pH, and round cells	Antioxidant properties of *N. sativa* oil	[45]
Alpinia officinarum	76 (n=31)	3 months	An increase in sperm count, the total number of spermatozoa with normal morphology,	Antioxidant and scavenging activity against the ROS via its phytochemical mainly including galangin	[46]
Sesame	25	3 months	Significant improvement in the sperm count and motility	Antioxidant	[47]
Crocus sativus L	20	10 days	Significant improvement in tip rigidity and tip tumescence; higher ILEF-15 score; increased number and duration of erectile events	Antioxidant	[48]
Panax ginseng	119	8 weeks	Higher ILEF-15 PEDT score	Vas deferens and seminal vesicles' increased NO synthesis, decreased sympathetic tone, and smooth muscle dilation	[49]
Tribulus terrestri and *Ecklonia bicyclis*	84	30 days	Improved ILEF-15 score; increase in testosterone	Activate the pathways of NO; ACE inhibitory activity	[50]

Spermatogenesis is a process by which spermatozoa (sperms) are formed in spermatogonia in the seminiferous tubule in the testes. The formation of spermatozoa from a single cell to the entire sperm takes seventy-four days to complete the process. At the age of fourteen years, the spermatogenesis process starts in males [51]. Various hormones are responsible for the process of spermatogenesis directly or indirectly. Numerous hormones that act directly or indirectly on spermatogenesis.

The hypothalamic neurosecretory cells secrete more gonadotropin-releasing hormone (GnRH), which in turn stimulates the anterior pituitary to secrete more luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Follicle Stimulating Hormone (FSH)

FSH is the hormone that triggers the beginning of spermatogenesis. FSH binds to Sertoli cells and spermatogonia and influences the growth of spermatogonia. Furthermore, FSH stimulates Sertoli cells' production and secretion of Androgen Binding Protein (ABP). The testosterone concentration in seminiferous tubules stays high because secreted ABP binds to testosterone. Testosterone is the hormone that stimulates the final step in the process of spermatogenesis. Sertoli cells release the hormone inhibin, after the process of spermatogenesis is over.

Testosterone

The male organ known as the testes produces testosterone, a steroidal hormone, from cholesterol. It is in charge of preserving spermatogenesis. Through the negative feedback mechanism of testosterone, hypothalamic neurosecretory cells suppress GnRH secretion. The key hormone for the development of the accessory sex organs, including the penis and scrotum, is testosterone (genital duct, seminal vesicle, and prostate gland). Due to testosterone, males develop a more masculine body, larger sex organs, longer bones, wider shoulders, longer pelvises, thicker skin, more evenly distributed hair, and a deeper voice.

Luteinizing Hormone

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The Cholesterol Side Chain Cleavage (CSCC) reaction, which increases the conversion of cholesterol to pregnenolone, is triggered when a receptor on a particular membrane on the surface of a Leydig cell binds to LH. This reaction increases cyclic AMP and calcium ions (Ca2+), protein kinase activation, phosphorylation, and protein synthesis. The cholesterol side chain cleavage (CSCC) reaction, which takes place in the mitochondria and is catalyzed by an enzyme complex, is typically regarded as the rate-limiting step in the steroid synthesis process. In Leydig cells, pregnenolone leaks from the mitochondria and is converted to a number of other steroids, including testosterone as the main end product.

Growth Hormone

For general metabolic processes in testis, growth hormone is necessary. It is also essential for the proliferation of spermatogonia.

Inhibin

Upon stimulating FSH, the Sertoli cell releases inhibin. A peptide hormone by the name of inhibin, inhibin inhibits the release of FSH through a feedback mechanism and, as a result, is crucial for spermatogenesis. There is an increase in inhibin secretion at the same time that the rate of spermatogenesis increases. A slower rate of spermatogenesis is caused by Inhibin's action on the anterior pituitary, which inhibits the release of FSH [52].

Results and Discussion

Sexual dysfunction is a major health issue nowadays. It is mostly affected by lifestyle, stress, and environmental factor or it may be genetic. This review main emphases on natural compounds with Aphrodisiac potential. Medicinal plants, extract/fraction, active constituents, or chemical moiety which enhances sexual drive or pleasure are termed Aphrodisiac. These compounds improve sexual dysfunction and behaviors. This review indicates the effectiveness of medicinal plants at the hormonal level and molecular level which improve sexual dysfunction like *Pedalium murex, Citrullus lanatus, Amaranthus spinosus, Piper, guineense*, etc. Furthermore, many Ayurvedic formulations have been investigated for their aphrodisiac potential. Many medicinal plants including *Withania somnifera, Mucuna pruriens, Tribulus terrestris, and Panax ginseng* proved their spermatogenic potential clinically.

According to the review, antioxidant effects are linked to the positive effects of medicinal plants on male reproductive function, which confirmed the ability of phytoconstituents to treat male infertility due to their presence.

The desire for sex, erection, mounting frequency, and ejaculatory frequency have all been treated with Ayurvedic formulations and medicinal plants. The accomplishment of cellular events is established by these features of male reproductive function.

In vivo studies on mammals typically last from a few days to several months, according to the review that has been presented. Additionally, the dosage of the medication varies, which may be brought on by the presence of phytoconstituents in a particular extract. Additionally, many medicinal plants continue to exist unexplored and are used by professionals in the trade. Therefore, substantiating claims about medicinal plants and defining their typical use is a huge challenge for researchers.

Conclusion

Herbal and Ayurvedic products are widely used in developing countries for the treatment of male infertility. Plants or products which have been clinically evaluated for treatment should be advised to treat the male infertility problem. Plants that are evaluated in vivo or in vitro for their claimed action should be encouraged for complete clinical evaluation of potential effects in the treatment of male infertility disorder. Also, the physicians treating male infertility must know those plants which are scientifically investigated and should combine traditional therapy with the modern one.

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