



# Role of Herbal Remedies in Male Fertility Management

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## Review Article

Volume 9 Issue 3

Received Date: July 09, 2024

Published Date: August 16, 2024

DOI: 10.23880/apct-16000244

## Abstract

Fertility management deals with both control of fertility as well as treatment of infertility of male and female partners. Ancient literature mentions the use of several plants/preparations for fertility management in humans. Many indigenous plants described in Ayurvedic and Unani texts have been used not only to control the fertility of humans but also to treat dysfunction of reproductive organs and sexual appearances. This could be because plant-based remedies are cheap, effective, and free from unwanted side effects. Further, their use ensure protection of privacy of the couple. Therefore, in this review, we have summarized most of the information dealing with the impact of plant-based drugs on male reproductive function, and their role in male fertility management.

**Keywords:** Fertility; Infertility; Spermatogenesis; Libido

## Introduction

Plants have been used since ancient times to regulate the fertility of both males and females, therefore, their role in contraception and conception becomes crucial. According to the World Health Organization (WHO) reports, 70%–80% of the world population confide in traditional medicine for primary healthcare [1]. In India, as well as across the world, plants and plant preparations have been regularly used to control fertility as well as to treat male-associated infertility problems as reported in ancient texts; this may be because of the ready availability and cost-effectiveness of the plant products, and essentially because of privacy issues of the users [2,3]. Further, plant-derived products are generally free from side effects.

The population of the world is increasing by 80 million per year and will likely reach 9.6–12.3 billion by 2100 [4–6]. The fast-growing population is a matter of great concern for developing countries including India since it leads to

severe problems such as degradation and pollution of the surrounding environment, slow economic growth, increase of poverty, malnutrition, unemployment, etc. Regulation of male fertility is an essential component of effective family planning methods due to the drawbacks of female-associated approaches. However, currently available methods of male fertility control are associated with side effects. As concerns regarding the side effects of existing male contraceptive methods, the development of additional male methods of fertility control can provide tremendous social and public health benefits. The biologically active and eco-friendly substances in plant preparations exhibit contraceptive effects in males due to spermicidal actions, suppression of spermatogenesis, altered forward motility, and fertilizing abilities of the sperm [7,8].

Male infertility is another serious issue and affects over 30 million men around the world; it is responsible for half of all cases of infertility [9]. Since male fertility largely depends on sperm count, viability, motility, and morphology, defects in

any of these factors can lead to infertility. Underdevelopment of the testicles, hormonal disorders of the reproductive system, elevated scrotal temperature, malfunctioning of the immune system, and irregular lifestyle, along with environmental and nutritional factors have been reported to affect sperm parameters and cause male infertility.

The present review article has been synthesized after a detailed literature search by consulting books, peer-reviewed papers, scientific databases such as Scopus, Science Direct and PubMed, and Google Scholar. Keywords such as antifertility, antispermatogenic, aphrodisiacs, conception, contraceptive, erectile dysfunction, fertility, infertility, and sterility concerning medicinal plants were used for the literature search.

### Plants in Fertility Regulation

The discovery of gossypol (isolated from cotton plant, *Gossypium* species) as a male contraceptive by Chinese scientists probably forced scientists to search out other medicinal plants with antifertility effects [10]. Chinoy et al. demonstrated the antifertility effects of crude extracts of *Carica papaya* Linn. (*C. papaya*) seeds [11]. Further investigation with *C. papaya* seeds has shown antifertility effects in different laboratory animals and is currently being extensively investigated in India [12,13]. Crude aqueous and chloroform extracts of *C. papaya* seeds caused sterile mating in rodents [14,15]. In addition, fractions isolated from *C. papaya* methanolic root extract adversely affected the fertility of male Wistar rats [16]. Likewise, extract of the root of *Tripterygium wilfordii* (Hook F.) showed reversible antifertility effects in male rats, while *T. hypoglaucum* exhibited antifertility effects in gerbils [17,18]. In addition to the plants mentioned above, a large number of other plants like *Barleria prionitis* Linn., *Ricinus communis* Linn., *Curcuma longa* Linn., *Aegle marmelos* Linn., *Albizia lebeck* Linn., *Hymenocardia acida* Tul., *Caesalpinia* sp., *Butea monosperma* Lam., *Calendula officinalis* Linn., *Leptadenia hastate* Pers., *Feronia limonia* Linn., *Tabernaemontana divaricate* Linn., *Citrus colocynthis* Linn., *Cuminum cyminum* Linn., *Hibiscus rosa-sinensis* Linn., *Dactyloctenium aegyptium* Linn., *Achyranthes aspera* Linn., *Abelmoschus esculentus* Linn., *Costus lucanusianu* Linn., *Andrographis paniculata* Burm f. [19-37], etc. have been worked out for their antifertility effects in males of different mammalian species in recent years. The search for medicinal plants and their products for the regulation of male fertility in India and other countries is still in progress with promising results [38]. Thus, plants hold a promising future in the regulation of male fertility [39]. There is, therefore, a need for exploring new plants/plant preparations for the control of fertility. In the present review article, we will discuss the antifertility investigation carried out for some important plants in India as well as

across the world.

### *Tripterygium wilfordii* (Hook F.)

It (family: Celastraceae) is commonly called as “thunder god vine” and grows extensively in southeast China. Various extracts from it are used to cure diseases in traditional and pharmaceutical Chinese medicines. It contains phytochemicals that are potent to relieve swelling, arthritis and other conditions.

**Antifertility investigation:** The root extract of *Tripterygium* exhibited reversible antifertility effects in rats [40]. Chinese investigators presented that a multiglycoside component of plant extract caused reductions in sperm motility and concentration in male patients [41]. The compounds viz. triptolide, triptidiolide, triptolidenol, triptchlorolide, 16-hydroxytriplide, and a compound known only as T7/19, isolated from *Tripterygium*, exhibited contraceptive effect [42]. Among these, Triptolide was identified as most promising contraceptive by the World Health Organization. Triptolide-treated rats in short-term studies showed reduced sperm counts, and absolute lack of motility with no effect on libido, body weight and reproductive hormones [43], and on the testis at the molecular level [44]. Triptidiolide, triptolidenol, 16-hydroxytriplide and T7/19 isolated from *T. wilfordii* extracts have recognized contraceptive effects, but these are yet to be systematically studied. *T. wilfordii* has not been tested as a contraceptive in men, and the existing reports come from studies on rodents, and retrospective studies of men taking a *Tripterygium* preparation for some other medical purpose. Therefore, evidence is lacking that *Tripterygium* is safe and effective as a method of birth control in men.

### Neem (*Azadirachta indica* Linn.)

It (family: Meliaceae) is a tree native to India with many medicinally valuable parts. The potential use of leaf extracts of neem as contraceptives is not a new idea; research on its use as a spermicide has been underway since the 1960's.

**Antifertility investigation:** Male mice when fed water crushed with fresh leaves of neem for 11 weeks impregnated fewer females with smaller litter sizes. The contraceptive effects were reversed within 6 weeks [45]. Neem oil acted as a spermicidal agent and inhibited sperm motility [46-48]. Polyherbal neem in a cream preparation showed contraceptive efficacy on intravaginal application and its safety was shown in monkeys [48]. The injection of minute quantities of neem oil into the vas deferens has been successfully tested as an alternative to surgical vasectomy [49]. Azadirachtin-A, isolated from *Azadirachta indica* (leaves) administered subcutaneously at 1.5 mg/kg b.w. (in

suspension of 50% DMSO) for 24 days to Wistar strain male albino rats showed a general decrease in reproductive organ weights, altered biochemical parameters and reduction in the sperm parameters with increased number of abnormal spermatozoa. [50].

### Papaya (*Carica papaya* Linn.)

It (family: Caricaceae) is a herbaceous succulent plant native to the tropics of the Americas but now is widely cultivated in other tropical regions of the world for its edible melon-like fruit, which is available throughout the year. Different parts of the plant are employed in the treatment of human and veterinary diseases in various parts of the world as an abortifacient, antiseptic for wound dressing, and as a cure for dyspepsia.

**Antifertility investigation:** The contraceptive property of papaya seed extract has been known since the early 1970's; The preparation from seeds has been shown to exhibit antifertility effects in laboratory animals and is being extensively investigated in India [51]. The antifertility effects of crude extracts of *Carica papaya* seeds in male mice were shown by Chinoy et al. [52]. Crude aqueous and chloroform extracts of *C. papaya* seeds caused reversible contraception in male rats and rabbits [14,53,54]. Treatment with lower doses of the crude extract of seeds led to a marked reduction in the quantity and quality of the sperm; the higher doses provided 100% effective contraception, but it also resulted in weight loss, possibly due to toxicity [54].

### Bitter gourd (*Momordica charantia* Linn.)

It (family: Cucurbitaceae) is an indigenous medicinal (especially for diabetes) and vegetable plant in the tropical and subtropical regions of the world.

**Antifertility investigation:** Petroleum ether, benzene, and alcohol extracts of Bitter melon when tested in rats (25 mg/100 g b.w. for 35 days) showed antispermatogenic activity, but the alcohol extract was more potent in its antispermatogenic, antisteroidogenic, and androgenic activities [55]. Yama et al. found similar results with methanolic extract of *M. charantia* seed in male Sprague-dawley rats [56]. In another study, seed extract of *M. charantia* was reported to affect spermatozoa in rats [57].

### Turmeric (*Curcuma longa* Linn.)

It (family Zingiberaceae), also known as Haldi, is a perennial herb throughout India and is widely used as an antibiotic in folk medicines and as spices.

**Antifertility investigation:** Plant-derived curcumin

(comprising of curcumin I, curcumin II, and curcumin III) has been shown to inhibit the 5 $\alpha$ -reductase enzyme, which converts testosterone to 5  $\alpha$ -dihydrotestosterone (DHT), thereby inhibiting the growth of flank organs in hamster. Curcumin also inhibits sperm motility in humans and has the potential for the development of a novel intravaginal contraceptive [58].

### Harad (*Terminalia chebula* Retz.)

It (family Combretaceae) carries several common names as black myrobalan (English), haritaki (Sanskrit and Bengali), harad (Hindi), harada (Marathi and Gujrati), and exhibits medicinal properties such as antibacterial, antifungal, antiviral, antidiabetic, antimutagenic, antioxidant, antiulcer and wound healing properties [59].

**Antifertility investigation:** The acetone, methanol, 50% ethanol, cold and hot aqueous bark extracts (300 mg/kg b.w. for 28 days) of harad caused non-uniform histologic alterations in testes and epididymes of treated mice, though, the aqueous extracts proved potent in inducing a severe reduction in the sperm production and fertility in albino mice compared to the other extracts of the plant [60]. The antifertility effect of Terminalia was reversible following treatment withdrawal without any apparent side effects [61].

### Jamun (*Eugenia jambolana* Lam.)

Jamun or Indian Blackberry is obtained from *Eugenia jambolana* synonymously known as *Syzygium cumini* Lam. (family Myrtaceae). It is considered a traditional medicine that has helped in controlling numerous lifestyle diseases such as diabetes, cardiovascular diseases, age-related macular degeneration, and others in India for many decades.

**Antifertility investigation:** Treatment of rats with low doses of oleanolic acid extracted from the flowers of *Eugenia jambolana* for 30 days resulted in reversible infertility with no changes in body weight or libido [62]. The contraceptive effect of *S. cumini* was reversed 14 days after ending treatment [63]. Normally, immotile sperm from testis are converted in fully functioning motile sperm in the epididymis. The sperm of rats treated with oleanolic acid emerge from the epididymis with decreased forward motility [63].

### China rose (*Hibiscus rosa-sinensis* Linn.)

*Hibiscus rosa-sinensis* (*H. rosa-sinensis*) Linn. is a common ornamental perennial shrub in Indian gardens. The large beautiful flowers of the plant are usually dark red and carry several common names such as China rose (English), Jasum (Hindi), Japa (Sanskrit), etc. The leaves, stems, roots, and flowers of *H. rosa-sinensis* have

been known to contain numerous medicinal properties like antihypolipidemic, antiproliferative, antioxidant, antimicrobial, antiinflammatory, and other pharmacological properties [64].

**Antifertility investigation:** Hibiscus has been known for its antifertility properties both in males and females [65,66]. Treatment with flower or leaf extracts of *H. rosa-sinensis* resulted in suppression of spermatogenesis and fertility in rats and mice as reported in different studies [67, 68, 69]. The roots of Hibiscus have also been used in post-coital antifertility effects in rats [69]. The antiimplantation activity of water extract from leaves of *H. rosa-sinensis* was also explored in rats [70].

### Plants in Fertility Improvement

The inability to have a child is a personal tragedy for couples suffering from infertility [71]. Infertility has become a challenging issue nowadays across the world. It is estimated that 50% of affected couples have male-associated factors as a cause of infertility [72] and 40–90% of male infertility is due to poor sperm production [73]. Male-associated infertility may be due to sexual dysfunctions, altered sperm parameters, or both. Alterations in spermatozoa include lack of sperm, too little sperm, abnormal morphology, and insufficient motility [72]. Although the causes of infertility in males are diverse, psychogenic endocrinal disorders, vascular injuries, and drug abuse are found as common cause of infertility in people. A variety of plant-based preparations are largely used to treat or relieve different aspects of male infertility such as the absence of libido, sexual asthenia, erectile dysfunction, ejaculatory and relaxation dysfunctions, loss of orgasm, and sperm abnormalities.

### Plants in treatment of erectile function

There are several plants which are used as decoctions and infusions in water, taken orally with in powder form to treat erectile dysfunction associated infertility, and to enhance virility and general weakness in men. In vitro and in vivo studies, have suggested that these plants may play a critical role in the treatment of infertility in men [74]. Viagra is a chief drug frequently used for the treatment of impotence and to cure erectile dysfunction. It is an indole alkaloid and hence it may be useful to evaluate plants that contain phytochemicals with similar structures. Aqueous extract of *Ruta chalepensis Lam.* (Common names: Herb of grace, Rue, Garden rue, Common rue) leaves (0.5, 1, and 2 g/kg for 30 days of treatment) increased the weight of testes and epididymides accompanied by improvement in the number, motility, and viability of spermatozoa as well as the levels of T and FSH in rats [75].

### Plants in treatment of libido

It is known that testosterone (T) and its byproduct dihydrotestosterone (DHT) motivate penile erection by maintaining the nitric oxide level. There are various reports on the effect of plant-based extracts or compounds on the levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels in humans [77]. Therefore these plants are very useful in modifying sexual functions in animals especially those suffering from hypotestosteronemia (lowered serum T).

### Plants in treatment of sperm parameters

Poor sperm quality as well as quantity is the most prevalent cause of male infertility [76]. The qualitative and quantitative parameters of spermatozoa is essential in male fertility. Sperm-associated infertility includes azoospermia (absence of sperm), oligospermia, asthenospermia and teratospermia. Plant extracts and derived compounds that promote count, motility, viability, and membrane integrity, and decrease sperm abnormalities need to be recognized and investigated. It is known that reactive oxygen species (ROS) harm sperm parameters; hence plants with antioxidant activities may enhance sperm quality [77]. In addition, Zinc and vitamin C are powerful antioxidants that increase fertilization rates significantly, enhance sperm quality, and prevent sperm agglutination thus making them more motile and with more forward progression [78]. Medicinal plants with identified antioxidant activities should be investigated as infertility remedies since antioxidants improve various aspects of male reproductive function such as spermatogenesis and steroidogenesis [77]. The identification of these powerful antioxidants in medicinal plants will be a useful tool in primary healthcare and also in bioprospecting these plants for the development of fertility agents.

### Toxicological Studies with Plants Used in Fertility Management

As stated above, plant-based products are generally free from unwanted side effects. The dose and durations of administration of herbal remedies for fertility control or infertility treatment are based on the preliminary findings, toxicological, haematological and histopathological studies of vital body organs, and according to the data mentioned in ancient texts. Most plants investigated for either antifertility potential or fertility improvement in males have not been thoroughly experimentally studied in humans. However, the findings in animals need to be translated to humans for a natural extract to be recommended for traditional use as an antifertility or infertility treatment agent.

## Molecular Mechanism of Action of Herbal Remedies

The potency of herbal remedies depends on their methods of preparation, and mode of consumption, including decoctions, extracts, semi-purified compounds, or purified active ingredients, etc., as inferred from in vitro and in vivo studies in laboratory animals such as mice and rats, and clinical studies in human. The mechanisms of action generally involve the testosterone pathway for stimulation or inhibition of spermatogenesis, oxidative status and inflammation, and apoptosis of germ cells in testis [79]. There are a few reports to explain the molecular mechanism of action of antifertility plants. In a study, mice were orally administered 50% ethanolic leaf extract of *Coccinia indica* (200 and 500 mg/ kg b.w./day) for 35 days to explore the antifertility efficacy and molecular mechanism of action. The activities of  $3\beta$ - and  $17\beta$ -hydroxysteroid dehydrogenases, western blot analyses of StAR protein, cytochrome P450scc enzyme and of caspase-3, germ cell apoptosis by TUNEL, and lipid peroxidation and antioxidant enzymes activities in the testis were assessed. The study showed that *Coccinia* treatment caused reversible suppression of spermatogenesis and fertility in albino mice, without producing detectable signs of toxicity. The suppression of spermatogenesis resulted from germ cell apoptosis due to deficiency of testosterone. The decrease in serum testosterone was because of the adverse effect of *C. indica* treatment on steroidogenesis and oxidative status in the testis [80,81].

## Discussion and Conclusion

Fertility management including contraception and treatment of infertility to achieve conception is an important component of reproductive health for both males and females. In India as well as across the world, there are several medicinal plants associated with antifertility properties in males. Further, many plants have been worked out to investigate their beneficial effects on male fertility. Thus, plants could be a source of agents for conception or contraception, or both. However, despite numerous studies, no plant or plant preparations have emerged so far with absolute effectiveness and without any toxicity. Further, very few contraceptive and conception drugs have been developed from plants, since their potentiality has not been determined accurately; furthermore, their mode of action has been beyond our knowledge until now because there are many problems in assessing plant extract including batch-to-batch variation and a lack of definite active fraction of the extract used for the drug development. Hence, the possibility of developing an effective contraceptive or conception drug from the plants is not guaranteed. However, despite above mentioned drawbacks associated with plant-derived products, researchers across the world still hold hope to

develop herbal remedies to control fertility as well as to treat infertility problems in males.

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