ISSN 0975 -8542

Journal of Global Pharma Technology

Available Online at www.jgpt.co.in

REVIEW PAPER

Use of Iranian Medicinal Plants Effective on Male Fertility Indices

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Abstract: This systematic review article was conducted to report medicinal plants that are effective on male fertility indices. To conduct this review, search terms fertility or pregnancy combined with medicinal plants, herb, and phyto were used to retrieve relevant publications indexed in ISI, PubMed, and Iranian scientific databases. Escanbil, *Fumaria parviflora* L., *Apium graveolens* L., *Achillea millefolium* inflorescence, *Urtica dioica* L., *Withania somnifera* L., *Phaleria macrocarpa*, *Satureja khuzestanica*, *Achillea millefolium*, *Malva sylvestris*, *Humulus lupulus* L., *Allium cepa*, *Petroselinum crispum*, *Carthamus tinctorius*, and *Zingiber officinale* were reported to be medicinal plants with fertility indices-promoting properties. Medicinal plants that are used in Iran affect hormonal compounds and other effective compounds on hormonal system as well as the proliferation and viability of sex cells due to their antioxidant properties, and therefore enhance fertility in human and animals.

Keywords: Physiotherapy, Infertility, Pregnancy, Iran.

Introduction

As one of the most common healthcare problems around the world, infertility imposes stupendous costs on families and challenges economic stability of healthcare system (1, 2). In Iran, infertility is considered one of the most important healthcare issues that affects the quality of life among affected people adversely and leads to psychosocial problems (3, 4). Although the reasons for infertility may be various and undetermined, oligozoospermia and asthenozoospermia are considered the most important causes of male infertility (5).

Treatment of infertility is one of the important challenges in the lives of infertile couples and the strategies of treating infertility should take into account certain issues such as age, side effects, treatment efficiency, and treatment costs in the patients (6), because treatments for infertility may be unsuccessful for several reasons, and therefore the patients' problems are likely to be doubled (7).

Therefore, efforts are being made to promote and find alternative treatments for infertility. Because of being economical and causing fewer side effects compared to synthetic drugs, medicinal plants can be potential suitable alternative therapies for several diseases (8-19). In this regard, different experimental and clinical studies have demonstrated the effects of these plants in addition to confirming their use in traditional medicine.

Studies indicate that in Iran, medicinal plants are much commonly used to treat different diseases (20-27) and also to the infertility (28). This systematic review was conducted to explain the status of Iran medicinal plants in preventing and treating male infertility via assessing publications on the effects of medicinal plants to enhance fertility indices (help treat infertility).

To conduct this review, search terms *fertility* or *pregnancy* combined with *medicinal plants*, *herb*, and *phyto* were used to retrieve

relevant publications indexed in ISI and PubMed. Then, the abstracts and data drawn from other resources were examined and only those studies that were conducted mainly to investigate the effects of the plants and their derivatives on male infertility in Iran and on medicinal plants native to Iran were included in analysis.

Results

There are several plants that have positive effects on fertility indices in laboratory animals and human, and there are different mechanisms for exertion of such properties.

Escanbil (Calligonum)

Calligonum is a plant from family Polygonaceae with antioxidant property due to the presence of quercetin and catechin. Therefore, this plant can play a role in sperm motility and viability. Administration with calligonum caused increase in the expression of the gene Catsper and subsequently improvement of sperm parameters in male mice (29).

Tribulus Terrestris (*Bindii*)

This plant is annual and occurs in different regions of the world. The effects of this plant were investigated on sex hormones and gonadotropins in laboratory mice with induced addiction to morphine. Administration with *T. terrestris*, as an antagonist, serves to reduce sex hormones except for follicle-stimulating hormone (FSH) in laboratory mice (30).

Fumaria parviflora L.

This plant has a special status in Iranian traditional medicine and contains antioxidant compounds that prevent the activity of oxidative substances, such that the ethanolic extract of this plant prevented reduction in testicular weight, serum testosterone level, the diameter of seminiferous tubules, the number of epididymal sperm, testicular content, superoxide dismutase, and glutathione peroxidase and therefore increased fertility in male mice with lead-induced testicular toxicity (31). *F. parviflora* leaf extract could increase fertility in male mice via enhancing androgenic activity and proliferation of sex cells as well as alkaloid compounds (with antioxidant property) (32).

Apium graveolens L. (Celery)

A. graveolens is from family Apiaceae. Administration with *A. graveolens* leaf extract after 30 days caused increase in testicular volume and seminiferous tubules diameter in mice. Besides that, the number of spermatocytes, spermatogonia, and spermatozoa increased, and therefore the process of spermatogenesis improved (33). In addition, oral administration of laboratory mice with *A. graveolens* leaf extract caused increase in the number of spermatocytes, Sertoli cells, and primary spermatocytes as well as the improvement of spermatogenesis (34). However, Modaresi et al. reported that different doses of hydroalcoholic *A. graveolens* leaf extract displayed different activities such that 100 and 150 mg/kg doses led to decrease in FSH level and dose-dependent adverse effects on pituitary in mice (35).

Achillea millefolium

A. millefolium is a flowering plant whose effect in cyclophosplamide-induced contraceptive side effects has been studied. Jalali et al. study showed that aqueous *A. millefolium* extract prevented decrease in testicular and epididymal weight in mice under treatment with cyclophosplamide and increased serum testosterone level, generally improving the process of spermatogenesis and fertility in Wistar rats (36). A study showed that degradation of sex cells and decrease in gonadotropins induced by cyclophosplamide were neutralized by administration with *A. millefolium* extract in laboratory mice (37).

Urtica dioica L.

The effect of this plant, commonly known as common nettle, was investigated on laboratory male mice with induced addiction to nicotine by Jalili et al. Intraperitoneal administration of the mice with hydroalcoholic *U. dioica* extract caused increase in testicular weight, the number and motility of the sperm, normal sperm morphology, serum testosterone level, and the diameter of seminiferous tubules after 28 days. Therefore, administration with this plant plays a role in increasing the quality of spermatozoa and sperm parameters (38).

Ginseng

Korean red ginseng has antioxidant and antiapoptotic compounds and can decrease epididymo-orchitis in laboratory male mice such that it causes increase in sperm concentration and motility and the number of normal sperms and therefore improves fertility indices (39). Gavage administration of laboratory mice with ginseng and vitamin E caused decrease in the number of sperm including viable sperm as well as malformed and abnormal sperm. In addition, the rate of fertility increased in male mice administered with ginseng and vitamin E via inducing antioxidant property in sex cells (40).

***Withania somnifera* L.**

W. somnifera is from family Solanaceae. A study demonstrated that oral administration with this plant caused increase in gonadotropin hormones in mice with already reduced fertility indices due to addiction to morphine, such that FSH and luteinizing hormone (LH) levels were modulated and estrogen and testosterone levels increased (41).

Phaleria macrocarpa

The effect of pulverized *P. macrocarpa* was investigated on laboratory mice fertility. This plant was reported to be one of the effective plants in treating infertility such that a study reported that the number of spermatogonial cells and the thickness of seminiferous tubules increased after the treatment and therefore it could be used as a complementary therapy (42).

Date palm pollen (*Phoenix dactylifera* L.)

P. dactylifera pollen is used to stimulate the libido and treat infertility. Treatment of infertile men with *P. dactylifera* pollen, as oral capsule, for two months was investigated by measuring sperm parameters. It was found that *P. dactylifera* pollen caused increase in the number and motility of sperm and improvement of sperm morphology. Therefore, *P. dactylifera* pollen can be used in the treatment of male infertility as a plant-based therapy (43).

Satureja khuzestanica

S. khuzestanica is from family Lamiaceae whose protective effect was investigated in preventing infertility in mice under treatment with cyclophosplamide. The essential oils of *S. khuzestanica* caused increase in plasma testosterone and sperm quality as well as decrease in DNA damage and oxidative stress (44).

Achillea millefolium

Akbarizadeh et al. investigated the protective effect of aqueous *A. millefolium* extract against cyclosporin on fertility indices in mice. *A. millefolium* neutralized the adverse effects of cyclosporin in reducing the number of sperm, sperm viability, laboratory fertility and led to significant increase in these parameters (45).

Malva sylvestris

M. sylvestris is a medicinal plant that has been used in Iranian traditional medicine for thousands of years and is from family Malvaceae. A study investigated the effect of this plant on sperm and soetmatogenesis phases in mice. According to the findings of this study, the number of primary spermatocytes and spermis increased significantly after treatment with hydroalcoholic *M. sylvestris* leaf extract (46).

***Humulus lupulus* L.**

H. lupulus flower extract causes increase in estrogen and testosterone as well as the number of spermatogonial cells, spermatocytes, and spermatids by phytoestrogenic compounds and stimulating LH secretion (47).

Allium cepa

The effect of oral administration with *A. cepa* extract was investigated on testicular tissue in mice. The results demonstrated that oral administration with raw *A. cepa* extract affected cell proliferation in mice testicular tubules and accelerated the trend of spermatogenesis in addition to influencing the structure of seminiferous tract (48).

Petroselinum crispum

Bastampour et al. found that the studied concentrations of *P. crispum* leaf extract caused modulation of LH and FSH, while the minimum and moderate concentrations of this extract caused serum levels of testosterone to increase and maximum concentration of this extract caused significant decrease in the level of this hormone (49).

Carthamus tinctorius

In Iran, *C. tinctorius* flower has pharmaceutical uses. Administration with *C. tinctorius* extract caused increase in serum testosterone concentration and negative physical self-control of testosterone secretion in mice (50).

Zingiber officinale

Pulverized *Z. officinale* rhizome caused increase in the rate and percentage of viability and motility of sperm and therefore infertility in laboratory mice (51).

Plant-based compounds

Rosmarinic Acid

Rosmarinic acid is a plant-based polyphenol whose effect was investigated on male mice exposed to electromagnetic field. The results demonstrated that serum testosterone level in mice under treatment with rosmarinic acid was higher than other groups, and this extract could be used to increase fertility with few side effects (52).

Traditional Prescriptions and Pharmaceutical Formulations

The effect of the combination of seven plants *Allium cepa*, *Zingiber officinale*, *Ocimum basilicum*, *Cinnamomum verum*, *Citrus sinensis*' peel, *Citrullus lanatus*' seeds and *Daucus carota*' seeds in a plant capsule was investigated on infertile men. After treatment with this capsule, the number and motility of the sperm as well as the number of normal sperm increased. Therefore, these plants caused improvement of sperm parameters through inducing antioxidant effect (53). A study investigated the effect of TOPALAF consisting of *T. Terrestris* fruit, almond kernel, watercress seeds, vegetable seeds, roots orchids, palm pollen, and fruit figs to enhance fertility in men. Treatment with this prescription caused improvement of sperm number and motility (54).

This review was conducted to report the plants and plant-based compounds that are effective on male infertility. Most research conducted on this subject has been animal studies. In most studies, both in vivo and in vitro, oxidative stress has been considered to be a factor for declined fertility and the studied plants cause increase in fertility due to antioxidant properties. Plant-based antioxidant compounds have been investigated for neutralization of reactive oxygen species (ROS) and reduction in adverse effects of oxidative stress via increasing peroxidases concentrations in different cells of the body and their effects have been reported (55-60).

The effects of these antioxidant compounds have been also investigated on sex cells. Indeed, the final product of the process causes increase in the number of healthy sperm that has significant effects on fertility (61). Moreover, the presence of plant-based antioxidants causes certain changes in gene expression and therefore improves fertility indices (29). However, it should be taken into account that small amounts of ROS are needed for natural sperm function for male fertility, but excessively higher amounts of threshold amount of ROS and associated metabolites can attack DNA, lipids, and proteins and disturb enzymatic system. This process leads ultimately to irreversible changes and cell death that cause decline in sperm parameters and therefore fertility (62). Therefore, determining the threshold level of ROS or their metabolites and the administered doses of antioxidants are important issues (63-67).

According to reviewed studies in male and laboratory male animals, some plants exert their effects due in different mechanisms (Figure 1).

Figure 1: Several mechanisms herbal medicine to increase fertility

It should be taken into account that stress and social pressure in infertility can lead to excessive consumption of medicinal plants; therefore, necessary measures should be taken to prevent adverse side effects of using medicinal plants that are effective on infertility and associated toxicities (68).

Conclusion

Medicinal plants that are used in Iran can increase fertility due to antioxidant compounds, hormonal compounds, and other effective compounds on hormonal system, and improvement of sex cells proliferation and viability and are therefore used as complementary therapies to modern treatments in fertility centers. It should be also taken into consideration that one plant may increase fertility in one gender but exert opposite effects on another gender.

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