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Review Article

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The Use of Medicinal Herbs to Treat Male Infertility in Jordan: Evidence-Based Review

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ABSTRACT

Male infertility accounts for about 8 – 14 % of couples worldwide with high dependence on conventional and alternative medicine for treatment. Herbal medicine may be used to treat sperm-related problems, enhance libido or improve hormone levels thus; it is crucial to report the herbal medicine being used by patients in Jordan and highlight their mechanism of action. We searched available ethnopharmacological articles in Jordan where plant use for male infertility was mentioned, collect herbal plants most commonly used and match the results with the reported one in the literature. In conclusion, eight medicinal plants were mostly recorded in Jordan folk medicine for male infertility treatment. All of them were studied in other areas with a result that they can enhance male fertility except for Raphanus sativus L. which acts as an anti-fertility plant. Patients should be encouraged to have proper information about the plants being used and further local studies should be performed to confirm the beneficial effect and safety of those herbal plants.

Key words: *Herbal medicine, Male, Infertility, Jordan, Sperm*

INTRODUCTION

Infertility is a worldwide clinical problem with an increasing incidence that affects around 8 – 14% of couples worldwide from which approximately 40 – 50 % is due to male infertility [1]. As there are no reliable figures for the prevalence of infertility in Jordan, however, in the middle east region, the total infertility prevalence rate is estimated at 12% [2, 3]. The World Health Organization (WHO) defined infertility as the failure of achieving pregnancy after one year of unprotected sexual intercourse, which could be classified into primary or secondary infertility [4].

Although there is an untutored understanding of the underlying reasons for male infertility, the most common explanations for such issues may vary from being a cause of the genetic disorder, low sperm production and semen quality criterion, blockage of reproductive tubules, erectile dysfunction, or male impotence, or a cause of lifestyle practices that can affect semen quality as smoking, increased caffeine intake, alcohol consumption, recreational drugs, obesity, stress and advanced marital age [5].

The efficiency of available marketed medications for infertility treatment may be not satisfying with many undesirable side effects, on the other hand, although Assisted Reproductive Treatment (ART), Intrauterine Insemination (IUI), and *in vitro* Fertilization (IVF) are more successful second-line treatments; they are expensive with expected side effects [6], that's why patients tend to refer to herbal medicine as an alternative remedy for male infertility problem.

For many years botanical medicine was being used to treat different diseases because they are cheap, available, and with tolerated side effects [7]. As a treatment for infertility, botanical medicine is used to get a healthy ovum and enhance spermatozoa production or to increase libido [8]. A cross-sectional study in Jordan that survived 438 infertile males revealed the high prevalence of the use of complementary and alternative medicine for infertility treatment with 43% using at least one of the alternatives and antioxidant therapies [9]. In previous ethnopharmacological studies which were conducted in different regions of Jordan, the most used plants to enhance infertility were *Lepidium sativum* L. [10], *Nigella sativa* L. [11], *Raphanus sativus* L. [11], *Peganum harmala* L. [12] and many others.

In this review, we first aim to summarize the pathophysiology of male infertility and then focus on the plants being used in Jordan to treat infertility with outcomes such as improved sperm quality, sexual functions, libido, and testosterone level. Thus, a complete review of the medicinal herbs highlighting the effective bioactive compounds in them according to their phytochemical classes and their explained mechanism of action improving male fertility will be presented.

Classifications of male infertility

Semen disorders

One of the foundational laboratory evaluations of male infertility is done through semen analysis. It is used as a tool to identify and classify any male factor infertility. A published detailed methodology and semen evaluation is placed by World Health Organization (WHO) [4]. The semen is evaluated for volume, pH, and leukocytes, while the sperm is assessed for count, concentration, motility, and morphology. In **(Table 1)**, we summarized various semen analysis factors and the normal range according to WHO [4].

Table 1. Semen Analysis and its normal range with lower reference limits according to WHO.

Factor	Normal	Lower Reference Limits (5th percentile)
Volume	2 to 6 mL	1.5 mL
Sperm count	> 20 million/mL	15 million/mL
Sperm motility	> 50% motile	40% motile
Sperm viability	> 75% viable	45% viable
Percentage of sperm with normal morphology	> 5.5% using the 1999 WHO strict criteria	4% using the 2010 WHO criteria

Pathophysiology of sperm disorders

Defects in seminal volume ejaculated

Hypospermia is diagnosed by having a seminal volume of fewer than 1.5 ml, thus resulting in a low volume of ejaculated semen. The causes of decreased semen production/volume are usually related to either the seminal vesicles or the prostate. In the most extreme cases, anejaculation is when there is no semen fluid released during sexual climax.

Dysfunction of the ejaculatory reflex is one of the major causes affecting seminal volume including an ejaculatory duct obstruction or retrograde ejaculation [13]. In other cases, ejaculatory duct obstruction (EDO) is the culprit due to an inflammation or infection within the ejaculatory ducts from conditions like varicocele and prostatitis [14]. It is evidenced to result in semen impairment including decreased semen volume and changes in seminal biochemistry. Finally, repeated ejaculation does result in lower sperm volume and the volume of semen decreases gradually over the years due to the aging of the male

Defects in sperm quality, such as abnormal motility or structure

Sperm motility is a requisite for normal fertilization enabling the spermatozoa to travel a long distance to meet and fertilize the oocyte. When a semen analysis is shown to have <32% progressively motile spermatozoa, it is considered asthenozoospermia; while absolute asthenozoospermia is when no sperm motility at all takes place, but they are viable, not dead. Reduced sperm motility is directly linked to defects in sperm's flagellum structure, and in other cases may be due to the presence of anti-sperm antibodies indicating an increase in sperm oxidative stress [15]. Antioxidant therapy has been shown to improve sperm quality [16], and vitamin D supplementation

may help with sperm motility [17]. In rare conditions, necrozoospermia, either the complete kind where all sperm are dead or the incomplete kind of 5-45% are still viable, have been reported with less than 1% prevalence among infertile subjects [18].

Lastly, according to WHO, the lower limit percentage of sperm with normal morphology is 4%, and any increase in sperm with abnormal morphology is referred to as teratozoospermia. This condition suggests an issue with spermatogenesis and defects in sperm maturation. Abnormal hormonal levels in the testis, including testosterone, might be the basis of this condition, and hormonal manipulation to normalize its low levels has been found an effective choice for treatment [19].

Defects in sperm count

A low sperm count, also called oligozoospermia, is when an inadequate quantity of sperm is found, specifically less than 15 million sperm per milliliter of semen. In its most severe form, azoospermia is characterized as the complete absence of spermatozoa. Defects in sperm count etiology can be subdivided into pre-testicular, testicular, or post-testicular causes. Numerous hormones play a critical role in the stimulation of spermatogenesis, including testosterone and FSH, while other hormones like prolactin and estrogen may have adverse effects [20]. In other cases, spermatogenesis is often normal but the presence of obstruction of the ducts or vas deferens can lead to low sperm count.

Hormonal imbalance

Endocrinological aspects of male infertility are briefly summarized. Testicular dysfunction and male infertility are sometimes due to hormonal imbalances caused by the pituitary's inability to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Male reproductive functions begin at the hypothalamic-pituitary-gonadal axis, playing a central and critical role by first producing the gonadotropin-releasing hormone (GnRH) in the hypothalamus. GnRH stimulates the pituitary gland to synthesize and secrete LH and FSH. Spermatogenesis is regulated by three important hormones, including testosterone. In the Leydig cells, LH stimulates the synthesis and secretion of testosterone and estradiol; while in the Sertoli cells, which are somatic cells in the testes essential for sperm production. FSH stimulates produce of androgen-binding protein (ABP), and a variety of growth factors [21]. The failure to produce and secrete the normal levels of these hormones will results in the disruption of testicular function and infertility , and various hormonal treatments have been used in treating male infertility [20].

Prolactin and thyroid functions are other key hormone. While prolactin levels are mainly associated with impotency rather than infertility [22], thyroid hormones' effect on spermatogenesis is not yet fully understood. Evidence shows that testis development, the process of spermatogenesis, and male fertility are all impacted by thyroid hormones, so an aberrant thyroid profile may alter sperm quality leading to fertility problems [23]. Therefore, endocrinological aspects of male infertility are critical and should be evaluated as a routine checkup for couples having difficulties conceiving.

Varicocele

Varicocele is an enlargement of the veins within the scrotum which limits the efficiency of circulating oxygen-depleted blood out of the scrotum from the testicles. There is an association between varicocele and infertility, with a 30% occurrence of varicocele in infertile couples [24]. Numerous studies looked into varicocele diagnosis and treatment for reproductive purposes and found it to be related to decreased sperm count, decreased motility of sperm, and an increase in the number of deformed sperm [24, 25]. However, it is still unclear how varicocele can affect and cause fertility complications.

Medicinal plants and their phytochemicals

Phytochemicals are secondary metabolites produced by plants during a specific metabolic process to give antioxidant, anti-inflammatory, antibacterial, pigmentation, or any other plant essential benefits. Those phytochemicals are classified into alkaloids, phytosterols, polyphenols, and terpenoids [26]. Flavonoids which are polyphenolic structures with the benzo-ɣ-pyrone scaffold **(Figure 1)** have six major subclasses (flavonols, flavones, flavanones, flavanonols, anthocyanins, and isoflavones), which differ by the degree of oxidation and unsaturation [27]. Flavonoids have been excessively studied because of their promising pharmacological activity in treating different male reproductive dysfunctions; the proposed mechanisms by which flavonoids can improve male infertility are: improvement of frozen sperm motility, improvement of sperm fertilization characters , reduction of any alteration can take place in the endocrine and replace testicular damages , and decrease germ cell apoptosis by improving testicular histology [28].

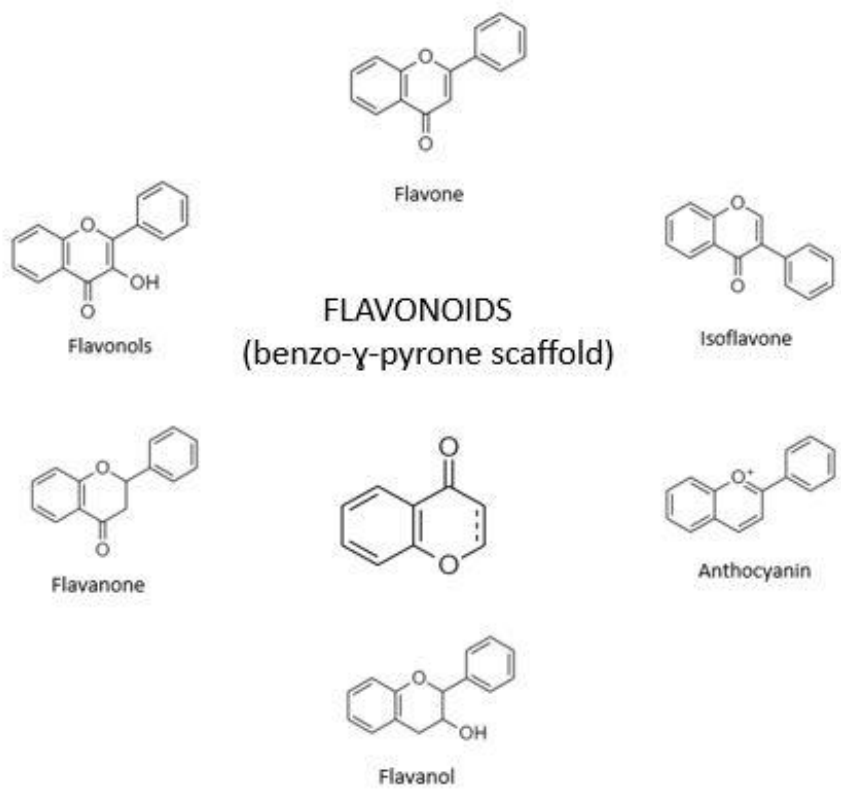

Figure 1. Flavonoids and the major subclasses' chemical structure.

Phytosterols are plant-derived fatty steroids containing a steroidal skeleton **(Figure 2)**, mainly phytosterols may appear as esterified or nonesterified structures of cinnamic acid or as glycosides. Previous studies showed that phytosterols can affect sperms positively by increasing their number, enhancing their motility, and reducing their oxidative stress response [29].

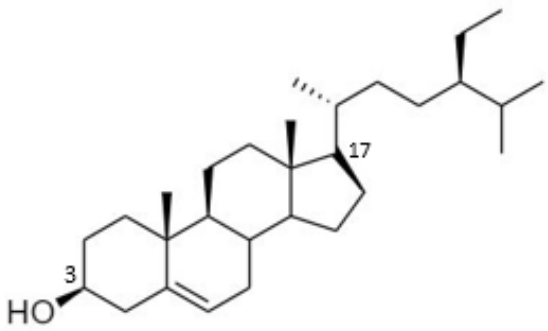

Figure 2. Phytosterols structure; a tetracyclic structure with a side chain on C17 and an essential hydroxyl group on C3.

Alkaloids are secondary metabolites containing a basic nitrogen atom, and some neutral or weakly acidic structures, and are classified into true alkaloids, proto-alkaloids, and pseudo-alkaloids [30]. Alkaloids showed a contrary effect on sperms and male fertility; a previous study that was conducted on nicotine's effect on male fertility ended up with a result that nicotine smokers may suffer from decreased motility, viability, and count of sperms [31].

Saponins are triterpinoidal or steroidal phytochemicals with sugar moiety and are characterized by their surfactant properties. The effect of saponins on male infertility may be summarized as being protective and regenerative against destroying agents , they can affect sperm mobility and viability thus improving male fertility [32].

Medicinal plants used in the treatment of male infertility

Allium cepa alliaceae

Onion is an old folk medicine that was used for its antibacterial, antioxidant, thrombolytic, hypolipidemic , and hypotensive activity [33]. In Jordan known as Basal, its bulbs or bulb juice is recommended by herbalists to treat prostate cancer [11]. Serah F Ige, *et al*., (2012) in its study obtained that *A. cepa* extracts improved the reproductive hormones (FSH and LH), and the sperm morphology, viability, and motility in male rats with reproductive dysfunction after being treated for 8 weeks with *A. cepa* extract, this was explained by the antioxidant activity of the extract that improved the oxidative status in their model [34].

The phytochemicals available in onion are high content of flavonoids, and low content of saponins, tannins, glycosides, triterpenoids, and sterols [35]. Quercetin the most abundant flavonoid in *A. cepa* plays a major role as an anti-oxidant; it can protect spermatozoa functional parameters from oxidative damage [33]. The antioxidant activity of *Allium cepa* extract was approved by another study that treated female rats after mating with *Allium cepa* juice for 21 days, the results showed that male pups of *A. cepa* juice treated female had increased sperm motility and viability when compared to the control untreated group which is a result of reduced testicular epididymal malondialdehyde (MDA) level and the protection against testicular oxidative stress [36].

Artemisia judaica asteraceae

Artemisia judaica L. known as Beithran is a perennial fragrant shrub that lives in the desert. Here in Jordan, it is used as a folk medicine to treat GI disturbances, heart-related diseases, diabetes, and sexual weakness [11]. A previous study that was conducted to find the effect of *A. judaica* extract on Diabetes showed that this extract can improve the testicular dysfunctions which may appear as a result of low insulin levels in such patients. Thus; this plant can prevent male hormone level disturbances which may in turn be crucial for spermatogenesis [37]. The active components of this plant are flavonoids, terpenes, alkaloids, tannins, saponins, sterols, and coumarins [38]. Flavonoids may have a promising anti-oxidant activity which can decrease reactive oxygen species responsible for sperm membrane damage or sperm DNA damage which may affect sperm morphological properties responsible for male infertility [38]. Another study that was conducted on male Wistar rats which were treated with *A. judaica* extract for 12 weeks showed a remarkable improvement in testosterone levels which has a significant effect on the spermatogenesis process, this positive correlation was explained by the antioxidant activity of the active phytochemicals in the extracts especially the flavonoids and terpenes [39].

Apium graveolens apiaceae

Celery or as known in Jordan (Krufs) is a strongly aromatic herb rich in flavonoids, triterpenes, sulphur glycosides, sterols, and coumarins [40]. A previous Jordanian study that was conducted on male rats for sixty days showed a significant decrease in spermatogenesis, sperm count, sperm motility, and testosterone level in a dose-dependent manner [41]. Another study that was run in Iran evaluated the effect of celery on male fertility and ended up with the result that celery can reduce fertility and decrease the number of offspring which may be a good natural medicinal plant choice for pregnancy control [42].

Lepidium sativum brassicaceae

Lepidium sativum L. (Habb Al Rashad) is a fast-growing annual herb known for its action on the male reproductive system. This plant is rich in glutamic and aspartic acid and also in stearic and palmitic acid also it is rich in phenolic compounds and terpenoids which can act as antioxidants [43]. A study by Asi *et al*., (2021) indicated that *Lepidium sativum* L. can prevent infertility in males by increasing the levels of testosterone, LH, and FSH, those results can be explained by the effect of *Lepidium sativum* L. on dopamine and acetylcholine both which can be related to sexual behavior [44]. The effect of the extract of Rashad on male fertility was explained by the increase in sperm production and the antioxidant activity which reduces the rate of sperm apoptosis [40].

Nigella sativa ranunculaceae

Nigella sativa L. (Habat Al-Baraka); is a plant that grows widely in Middle Eastern countries. The black seeds are bitter containing different phytochemical structures such as phenolic compounds alkaloids and essential fatty acids [45]. Here in Jordan, it is recommended to use *Nigella sativa* L. to improve sexual impotence [46]. The pharmacological effect of this plant on male infertility depends on increasing testosterone and follicle-stimulating hormone (FSH) levels which in turn will affect sperm quality, concentration, and motility in a positive way [47]. A randomized, double-blind, placebo-controlled clinical trial studied the effect of consuming 5 ml *N. sativa* oil on semen quality and showed that the parameters of semen were improved as an effect of the unsaturated fatty acids available in the oil [48]. Another *in vivo* study which applied *Nigella sativa* extract to male rats for 60 days

showed that rats who received a high dose (400 mg/kg) of extract had significant improvement in fertility parameters and sperm count [49]. A study that was conducted by Mohammad *et al*., (2019) revealed that black seeds extract can trigger spermatogenesis hormones in the pituitary gland, and thus, improves reproductive organs' weight and enhance sperm motility [50]. Overall the extract and the oil of this plant can improve spermatogenesis and testicular tissue [51].

Peganum harmala zygophyllaceae

Harmal; is a wild-growing flowering plant in the Eastern Mediterranean area. Alkaloids are the main active metabolites that occur in the seeds and roots of the plant and they possess hypothermic and hallucinogenic properties [52]. After treating rats for 56 days with the ethanolic extract of the harmal seeds the results showed that harmal can improve the gonads and accessory sex organs' weight, and also, it can boost semen quality [53]. Although it is widely used among the Jordanian population as an aphrodisiac and fertility-promoting agent, a study in Jordan that was performed on male albino rats showed that *Peganum harmala* decreased fertility by decreasing reproductive organs weight and decreasing the main hormone of spermatogenesis, also sperm motility and density were decreased [54].

Raphanus sativus brassicaceae

In Jordan *Raphanus sativus* L. (Fejil) is widely used for its aphrodisiac activity besides its positive effect on male fertility, the part being used is the leaves and seeds of the plant which are rich in alkaloids, flavonoids, saponins, and coumarins [11, 55]. Male fertility hormones level increases significantly when using the plant extract and this can be influenced by the saponin content that can boost the testosterone levels in the body [56]. Another study that was performed on male Wistar albino rats for 30 days manifested controversial results where sperm motility and spermatozoa number in rats treated with radish extract were decreased because of the androgenic synthesis alteration this confirms the anti-fertility activity of *Raphanus sativus* L. [57].

Trigonella foenum-graecum leguminosae

Fenugreek (Hilba) contains fibers, flavonoids, saponins, proteins, carbohydrates, fixed oils, amino acids, volatile oils, polysaccharides, and alkaloids in leaves and seeds thus; it can possess many health-related pharmacological activities such as antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, hepatoprotective, anti-ulcer and many others [58]. On the other hand, the extract of the seeds exerts an anti-fertility effect. This was approved by the decreased weight of reproductive organs and the altered sperm count and motility [58]. Another study that was performed on male albino rats approved the direct interference of fenugreek seeds on spermatogenesis and sperm count and viability which means fertility was reduced in rats treated with fenugreek seeds [59]. An opposite conclusion was reached by Kaur *et al*., (2020), which furnished evidence that fenugreek can solve testicular damage problems by the antioxidants available in the plant [60].

CONCLUSION

This review revealed that some medicinal plants are being used to treat male-related infertility problems. There was much-missing information about the method of use and the exact infertility condition treated with the plant. On the other hand, all the preclinical and in vivo studies available about the plants are from other regions and this may give plants with different phytochemical compositions or concentrations besides the differences in ethnicity. Therefore, more local studies should be performed to study the pharmacological effect end the safety of those plants after being cultivated and collected from Jordan, then patients should be provided with the best method of use and duration of the plant.

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