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Infertility is a disease of the reproductive system. It makes a person unable to have children. It can affect a man, a woman, or both. Male infertility means that a man has a problem with his reproductive system. It means you cannot start a pregnancy with your female partner. Since they haven't been able to produce a child despite engaging in frequent, unprotected sexual activity for a year or longer, nearly one in seven couples are infertile. Up to half of these partners are affected to some extent by male infertility. Low sperm production, abnormal sperm function, or obstructions that impede sperm delivery can all contribute to male infertility. Male infertility may be brought on by illnesses, accidents, chronic health issues, lifestyle decisions, and other factors. Male infertility is a condition that can be stressful and upsetting, but there are several treatments available. Male infertility is the primary health issue with economic, psychological, and medical attributions. Moreover, it is characterized by an inability to produce a sufficient amount of sperm for the fertilization of an oocyte. Dietary nutrients (DN) have a great effect on male reproductive potential.



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Herbal Medicines for Men Infertility

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Abstract:

Infertility is a disease of the reproductive system. It makes a person unable to have children. It can affect a man, a woman, or both. Male infertility means that a man has a problem with his reproductive system. It means you cannot start a pregnancy with your female partner. Since they haven't been able to produce a child despite engaging in frequent, unprotected sexual activity for a year or longer, nearly one in seven couples are infertile. Up to half of these partners are affected to some extent by male infertility. Low sperm production, abnormal sperm function, or obstructions that impede sperm delivery can all contribute to male infertility. Male infertility may be brought on by illnesses, accidents, chronic health issues, lifestyle decisions, and other factors. Male infertility is a condition that can be stressful and upsetting, but there are several treatments available. Male infertility is the primary health issue with economic, psychological, and medical attributions. Moreover, it is characterized by an inability to produce a sufficient amount of sperm for the fertilization of an oocyte. Dietary nutrients (DN) have a great effect on male reproductive potential. Observations have indicated that adding DN may protect or treat male infertility. This criticism aims to scrutinize the DN, such as omega-3 fatty acids, vitamins, minerals, and other phytochemicals, in enhancing the semen attributes, sperm bioenergetics, and sperm functionality in male infertility. Diets that are rich in omega-3 fatty acids affect sperm quality and maintain the sperm membrane and mitochondria stability. An administration of phytochemicals caused an escalation in sperm mitochondrial function and a decrease in oxidative damage. For millions of couples, not being able to conceive a child is a devastating occurrence in their lives, and many of them experience personal frustration. Equally affecting both parties is the issue of infertility in relationships. In many

countries, medicinal plants have been used in combination with other techniques to address male infertility issues. These herbs are used as medicines to address erection problems, libido dysfunction, and sexual atrophy. Herbalism is the primary form of treatment in our healthcare system and offers infertile couples a therapeutic option that is both cheap and accessible. Therefore, the majority of the information pertaining to the beneficial impacts of plant extracts on the mammalian reproductive system has been summarized in this review.

Keywords: Male Infertility, Herbal Medicine, Reproductive System.

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Introduction:

Infertility is recognized as the inability to conceive after 12 months of sexual practice without using contraception [1]. Infertility is one of the problems of human society. According to the World Health Organization (WHO), 15–10 percent of couples have experienced some form of infertility problems, and 40% of these problems are due to male factors [2, 3]. Reproductive ability in the male contains the production of semen containing normal spermatozoa (quality) in an adequate number (quantity), together with the desire and ability to mate [4]. Different reasons are involved in the occurrence of male infertility, such as genetic disorders, genital duct obstruction, varicocele, decreased sperm production, decreased semen quality parameters, erectile dysfunction, and male impotence [2]. Studies have shown that semen parameters in 25 to 40% of young males are below the standard of the World Health Organization [5]. Different treatments like surgery, chemicals, herbal drugs, and laboratory methods are available to help with fertility. According to several studies, several botanical medicines have a positive effect on sperm parameters [6]. Herbal plants have been famous since ancient times, and in recent years, a multilateral approach has appeared to use herbal medicines along with the medical care they get from their health care provider [7, 8]. Alternative therapies, such as herbal plants have more benefits since they are less invasive and less costly physical and emotional treatment compared with other methods. The aim of this book is to critically review the available literature on herbal medicines and their possible roles in the treatment of male infertility. In addition, male infertility is frequently instigated by complications in the ejection of semen, sperm production, absence or inferior sperm, sperm kinetics, and sperm abnormalities. Commonly, based on the reports of ASRM, 2014, the term “Infertility disorder” is definite as “the incapability to conceive

after one year of unprotected intercourse or six months for women aged 35 years or older". Clinically, infertility is well defined as a couple's failure to conceive subsequent one year of vulnerable intercourse without pregnancy [9].

Every year, scientists observe a huge decline in fertility worldwide [10]. The World Health Organization (WHO) states that there are 45–80 million infertile couples internationally [11]. In the UK, it is assessed that one in seven couples experience complications conceiving, with male-issued infertility accounting for 40–50% of all infertility cases [12]. As referenced by many authors, human male fertility is prejudiced by numerous issues, such as low sperm production, reduced sperm motility, higher sperm abnormalities, medical influences (cancer and pelvic inflammatory illness), non-modifiable influences (e.g., age, gender, and genetics), and utmost significantly adjustable lifestyle issues, e.g., alcohol, nutrition, stress, overweight, physical activity, smoking, and long-term use of preventives. Other risk factors for male reproductive dysfunction include gonadotropins such as chemotherapeutic agents, radiation exposure, and a variety of pharmaceutical agents that act either as direct spermatozooids or through a steroidal pathway. Common drugs known to impair male fertility include cimetidine, sulfasalazine, nitrofurantoin, ethanol, cannabis, and androgenic steroids. Whether nicotine results in impaired male fertility is controversial; however, because of its negative effect on erectile function, nicotine use is discouraged in men attempting to impregnate their partners. A male who does not have biological offspring and who presents for reproductive evaluation is labeled as having "primary infertility," whereas one who is unable to impregnate his partner but who already has biological children is referred to as having "secondary infertility" [13-16].

A physical examination of the scrotum, including the testes, is essential for any male fertility workup. It is useful for detecting large varicoceles, undescended testes, and absence of vas deferens, cysts, or other physical abnormalities. Checking the size of the testicles is helpful. Smaller-sized and softer testicles along with tests that show low sperm count are strongly associated with problems in sperm formation. Normal testicles accompanied by a low sperm count, however, suggest possible obstruction. Complementary therapies for infertility have received growing attention in recent years and various antioxidants, nutritional approaches, and medicinal plants have been proposed for the treatment of fertility problems in infertile and subfertile couples [17]. 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 [18]. Following men's increasing interest in effective herbal treatments for infertility, complementary approaches to infertility treatment have received growing attention [19]. 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 [20]. The World Health Organization (WHO) encourages the use of medicinal plants, and suggested researchers define the rational use of medicinal plants as a source of new treatments [21]. The 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 several others alter the secretion of hormones by the testicles [22]. The flavonoids and phenolic compounds in some plants serve as potent antioxidants against oxygenated free radicals. They protect the sperm against free radicals and improve sperm quality

and fertility parameters [22]. However, according to the World Health Organization (WHO), despite the wide use of herbal medicines, scientific knowledge of 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. Therefore, 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.

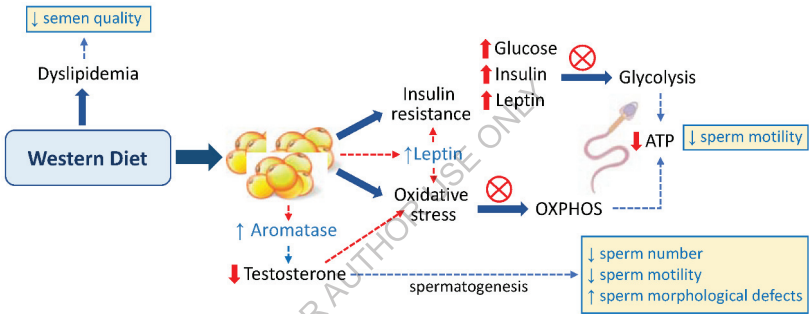


Figure 1. Effects of the Western diet on sperm quality.

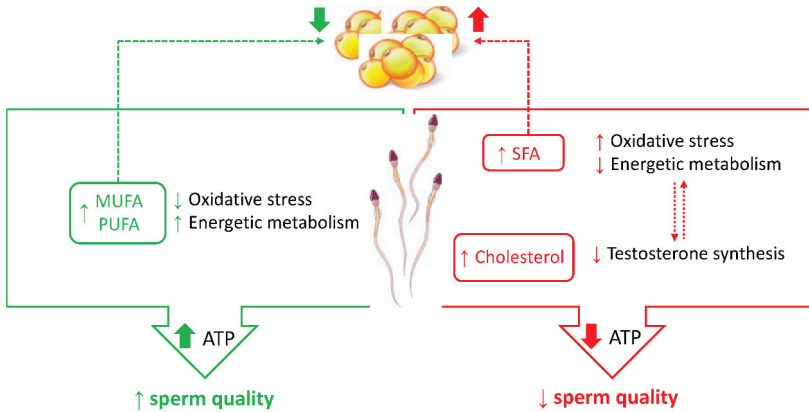


Figure 2. Effects of dietary fat on sperm quality.

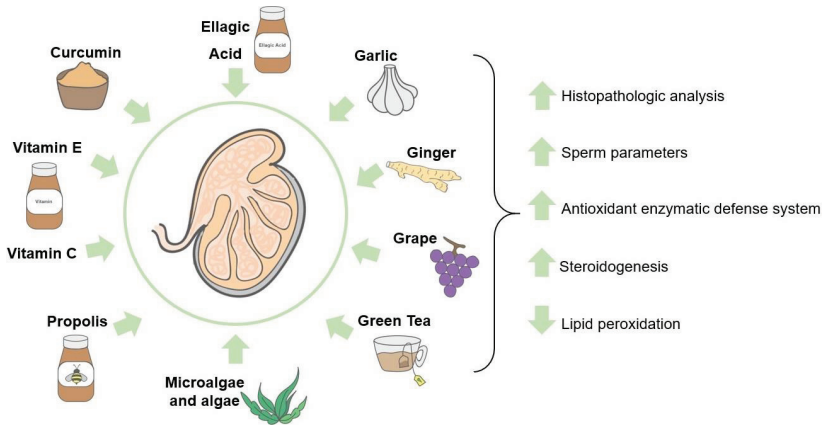


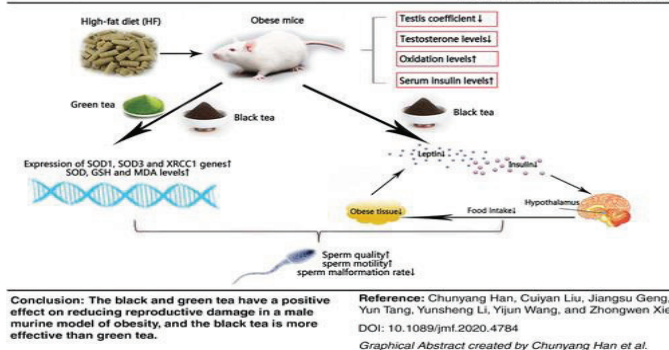
Figure 3. Graphical Abstract

Tea(*Camellia sinensis*)

Green tea (*Camellia sinensis*) is one of the most popular beverages in many countries. The main reason for this interest is the awareness of people about the therapeutic properties of this drink. Tea contains, a group of catechins that include catechin, epicatechin, gallic acid, epigallocatechin, catechin gallate, epicatechin gallate, gallic acid gallate, and epigallocatechin gallate, and vitamins, minerals polyphenols, flavonols (theaflavins, thearubigens), adenine, theobromine, theophylline, xanthine, gallotannin, small amounts of aminophylline and a yellow volatile oil which is solid at room temperatures and has strong aromatic smell and flavor [23]. The current research has shown that both green and black tea contain flavonoids such as quercetin, kaempferol, and myricetin, which have strong anti-toxic and anti-carcinogenic properties. Green tea

extract (GTE) had an inhibitory effect on cadmium (Cd) toxicity by decreasing the formation of lipid peroxidation products [24]. level, and minimal histological changes in the testes of rats that were treated with Cd + GTE. Catechin normalizes lipid peroxidation in Cd – poisoned rats' testes [25]. A significant decrease was observed in thiobarbituric acid reactive substances (TBARS) content of rat testis, fed with black tea after 3, 6, 9, and 12 months. The components in black tea provide antioxidative effects against CCl₄- induced toxicity in the testes of male rats since it could decrease carbon tetrachloride (CCl₄-) induced lipid peroxidation [26].

Another study showed that both fermented rooibos and green tea significantly increased the superoxide dismutase (SOD) activity in the tissue of the testis and significantly decreased lipid peroxidation (TBARS) in this tissue, measured as malondialdehyde (MDA). These studies showed that the antioxidant defense systems of testicular tissue protect the testes against oxidative damage, reduce free radicals effectively, and decrease damage to spermatogenic cells [27]. It has been reported that catalase, SOD, peroxidase activity (POD), and glutathione peroxidase (GSH-Px) act as defense systems against reactive oxygen species [28]. These results suggest that fermented rooibos and green tea can be used as supportive therapy for male infertility, in cases where oxidative stress is involved [29].



Green tea can also protect against the toxic effects of some drugs, such as doxorubicin, an anthracycline antibiotic [30]. The administrations of two different green tea extract concentrations (200 mg/kg and 500 mg/kg) against doxorubicin-induced toxicity seemed to ameliorate the histological findings and increased sperm parameters (concentration and mobility), the Sertoli cell index (ratio between germ cells number and Sertoli cells number), and telomerase activity in both concentrations [30]. Several studies have indicated the beneficial effects of green tea, though there are also reports of relevant side effects, such as hepatotoxicity and gastrointestinal disorders as well as drug interactions [31].

A study on pump workers exposed to benzene toxicity, showed that daily drinking of six tea cups for 6 month can significantly improve the antioxidant status [32]. In another study on humans, it was shown that the consumption of 6 g of green tea in 600 mL of water for 7 days could increase plasma glutathione and improve the post exercise increase in lipid hydroperoxidase [33]. Heat-treated rats show a decreased number and significant deteriorated sperms but GTE can decrease the harmful

effects to increase the number and motility of spermatozoa especially after 28 days of treatment [34].

Carrot

Daucus carota commonly known as "Carrot" belongs to the family of Apiaceae, a useful vegetable being used worldwide. Many studies have been done on chemical composition of this plant and a large number of active ingredients such as volatile oils, steroids, tannins, flavonoids, and caroten have been isolated. It has been reported that carrot can increase the potency in men, while in women it stimulates menstruation, and seeds are more effective than other parts of the plant [35]. The extract of carrot seed has more antioxidants and can increase the sperm reserves in cauda epididymis (CESR) [36]. In addition, co-administration of this extract with gentamicin can counterbalance the negative effect of gentamicin on the sperm count demonstrated in studies [35, 37]. Spermatogenic activity and the number of developing germ cells were also increased after exposure to carrot seed extract indicating the positive effect of the extract on meiosis [35]. Testosterone level was increased after carrot seed extract administration, showing enhancing effects of this extract on spermatogenesis hormones. It is likely that the use of this plant could be an effective and safe way to decrease the toxic effects of chemicals on the reproductive system and infertility in males [35].

Garlic

Garlic (*Allium sativum*) has been used as a medicine world-wide since ancient times [36]. Diallyl tetrasulphide is the bioactive organosulphur component of garlic, which have antioxidant effects [37]. Garlic contain a wide variety of phytochemicals and microcomponents such as trace elements, vitamins, fructans, flavonoids, and sulphur compounds, which

can effectively scavenge free radicals [38]. Some studies have reported that garlic harmsthe function of testes and has spermicidal effects on spermatozoa but some others demonstrated the opposite effect [39]. Rats fed with 10%, 15% or 30% *Allium sativum* (AS) containing diet, showed a significant increase in the number of empty seminiferous tubules in testes and a decrease in the level of testosterone. Male rats fed with crude garlic showed damaged testicular function and spermatogenesis. Also, a decreased prostate weight was associated with a reduction in citric acid content in rats fed with 30% garlic [39]. Yuriko et al demonstrated that the increased concentration of testicular testosterone after feeding rats with 8 g of garlic powder was due to an increase in luteinizing hormone (LH) level in plasma. Indeed, crude garlic and garlic powder may have the same active compounds [40]. Rats fed with garlic water extract over 3 months showed an increase in epididymis spermatozoa [41]. Dixit and Joshi reported a spermatogenesis stop at the primary spermatocyte stage with 50 mg of oral administration of garlic powder for 70 days [42]. Ola-Mudathir et al. indicated that aqueous extracts of garlic caused an increase in the catalase [43] activity and protects the testis and spermatozoa against cadmium toxicity [37]. Some of these different results might be due to the type of preparations used like garlic powder [40, 42], water extract [41], aged garlic, raw garlic juice and heated garlic juice [44] or the doses and the method of administration (gavage, i.p. injection, ad libitum), so more research in these area is needed.

Ginger

Zingiber Officinale commonly called ginger belongs to the family of Zingiberaceae. It contains several compounds including acid, resins, vitamin C compounds, folic acid, inositol, choline and pantothenic acid, gingerol, sesquiterpene, vitamin B3 and B6 volatile oils and trace elements [Ca, Mg, P and K] [45]. All major active ingredients of *Z. officinale*, such as Zingerone, Gingerdiol, Zingiberene, gingerols and shogaols, have antioxidant properties [46]. Besides, other studies showed that ginger oil has protective effect on DNA damage against Hydrogen Peroxide (H₂O₂) and might decrease oxygen radical and could be used as an antioxidant [47, 48]. This plant has been considered as a safe herbal medicine with few side effects [49]. Both antioxidative and androgenic activity of *Z. officinale* have been reported in animal models [50]. Ginger has been shown that decreases lipid peroxidation and increases glutathione content in blood of rats by maintaining the activities of the antioxidant enzymes; superoxide dismutase (SOD), catalase [43] and glutathione peroxidase (GSH) in the rat testes [45]. Morakinyo et al. (2008) reported that *Zingiber Officinale* have a beneficial effect on male reproductive functions in rats, which are confirmed by other studies on the increased sperm counts, motility, testosterone, and decrease malondialdehyde levels [51]. Ginger has been previously shown to stimulate spermatogenesis [45]. It was also observed that the administration of ginger can significantly increase testosterone level in plasma [52]. Co-administration of ginger and arsenite restored the reproductive organ which might be due to the androgenic activity of ginger [45]. The results of other studies also showed that ginger could increase cauda epididymis sperm reserves (CESR) of rats by increasing testicular spermatogenesis. It was indicated that the administration of ginger can conquer gentamicin reproductive toxicity on sperm count. Ginger administration caused a clearly increased level of testosterone in

the rats even in spite of receiving 5 mg/kg/day gentamicin comparing with the control or gentamicin-treated groups [53]. It has been demonstrated that, ginger have an antioxidant and androgenic activity in dose of 50 mg/kg/rat, which have positive effects on spermatogenesis and sperm parameters in rats [50]. In another study, administration of 50 mg/kg/cock and 100 mg/kg/cock ginger to 28, 32, 36, 40 and 44 weekage rats, significantly increased the concentration and motility of sperms in ejaculation volume. In this study, administration of 5% and 10% ginger for twenty consecutive weeks, significantly increased the sperm motility and viability in both experimental groups compared with the control group [54]. In the other study, administration of 1000mg/kg to rats for 28 days showed a significant weight increase compared to the control group. The highest reduction of MDA level was for the (1000mg/kg) 28 days treatment regimen and the lowest was for the (500mg/kg) 14 days treatment. Caudal epididymal sperm count and motility were significantly increased after 14 and 28 days treatment in a dose and duration-dependent manner compared with the control group [51]. Amin et al showed that *Z. officinale* could increase the activities of testicular antioxidant enzymes and restoresperm motility of cisplatin-treated rats beside protection against cisplatin-induced testicular damage [55]. We recently showed that ginger extract at doses of 300 and 600 mg/ kg BW has a positive effect on recovery of spermatogenesis in adult rats after cyclophosphamide (CP) treatment. Also, we found that co-administration of this extract with CP can counterbalance the negative effect of CP on testis parameters demonstrated in our study [56].

Rose Oil

Rose oil is extracted from rose flowers by steam distillation. Rose oil is a lucid, light yellow, and volatile oil. There are five major constituents in oil such as citronellol, geraniol, nerol, linalool, and phenylethyl alcohol [57]. Based on the results of aldehyde/carboxylic acid test that is used to show long-term antioxidant activity, Wei & Shibamo to have reported that rose oil has an antioxidant activity almost equal to α -tocopherol, which was used as a reference [58]. The increase in number and motility of sperm and Leydig cell counts, seminiferous tubule diameters, and decreasing the number of abnormal sperm show the positive effects of Rose oil on the male reproductive system. Another study showed significant histopathological improvement in testes and total testosterone levels of the rats exposed to rose oil and formaldehyde (FA) compared to the rats exposed to FA alone [57].

Capsaicin

Capsaicin (CAP 8-methyl-N-vanillyl-6-nonamide) is an irritating substance in hot peppers of the genus *Capsicum*, which is widely used as food additive throughout the world. It has been reported that Capsaicin inhibits DNA synthesis in the testes of mice when injected intraperitoneally. Also, CAP can persuade apoptosis in two different spermatogonial stem cell lines in vitro [59]. In another study, the weight of cocks fed with a diet containing 1% red hot pepper (10 g/kg diet), were decreased, while the weight and length, width and wall thickness of seminiferous tubules were increased, and spermatogenesis were completed earlier. It is shown that CAP stimulates spermatogenic cell proliferation in developing roosters [60]. Koul and Kapil, reported that piperine, isolated from *P. longum*, decreases the lipid peroxidation, enzymatic leakage of alanine amino transferase (GPT), alkaline phosphatase (AP), and prevents glutathione depletion and total thiols in

intoxicated mice [61]. *P. longum*-treated mice showed a significant increase in the weight of testes, cauda epididymis and seminal vesicles, indicating an androgenic activity of the extract. In the extract-treated animals, the sperm number and motility were significantly elevated as well [60].

Cinnamomum

Cinnamomum (family of Lauraceae) species contain volatile oils, tannins, terpenoids, mucilage, oxalates and starch. Different chemical constituents of *C. zeylanicum* are known to have significant germicidal, antiulcerogenic and cytotoxic effects. In a study, the extract of *Cinnamomum* increased the weight of testes, caudae epididymides and seminal vesicles in the treated male mice, indicating a possible stimulation of hormonal levels in the animals. Also, the sperm count and motility of the treated animals were significantly higher than the control group [62]. In another study, oral administration of *C. zeylanicum* extract at 500 mg/kg to diabetic male rats for 65 days increased the weight of testes and seminal vesicles, improved semen quality and quantity, and increased serum insulin and testosterone levels. It also decreased the degenerative lesions seen in the testes of diabetic rats [63].

Fenugreek

Fenugreek (*Trigonella foenum-graecum*) is a herb belonging to the family of leguminosa [64]. Fenugreek seed contains 45-60% carbohydrates, mainly mucilaginous fiber (galactomannans); 20-30% proteins high in lysine and tryptophan; 5-10% fixed oils (lipids); pyridine-type alkaloids, mainly trigonelline [0.2-0.36%], choline (0.5%), gentianine and carpaine; the luteolin, flavonoids apigenin, quercetin, orientin, isovitexin and vitexin; free amino acids, like 4-hydroxyisoleucine (0.09%);

histidine, arginine and lysine; calcium and iron; saponins (0.6-1.7%) ; glycosides yielding steroidal sapogenins on hydrolysis (yamogenin, neotigogenin, tigogenin, diosgenin) ; cholesterol and sitosterol; vitamins A, B1,C and nicotinic acid; coumarin compounds and 0.015% volatile oils (nalkanes and sesquiterpenes) [50]. Recently, Sakr et al, reported that fenugreek seeds prevent adriamycin-induced cytogenetic and damages of testis in albino rats [65]. Another study showed that oral administration of fenugreek seeds extract improves the histological changes caused by carbendazim and suppress the oxidative stress (OS) as indicated by decrease of lipid peroxidation and increase of activity of SOD and CAT. The antioxidant effect of fenugreek is ascribed to the presence of flavonoids and polyphenols. Thus, the effect of fenugreek against testicular toxicity of carbendazim may be associated with the antioxidant activity of the constituents [64]. It has been reported that the polyphenolic extract of fenugreek seeds has an antioxidation effect in vitro [66]. A study showed that in rabbits, a fenugreek seed powder containing diet (30%) for 3 months could significantly decrease male testis weight [~25%] and sperm concentration [~43%] , indicating a toxic effect of fenugreek seeds on seminiferous tubules and the interstitial tissue (Leydig cells) . The negative impact of fenugreek seeds on the male structural and functional integrity of testicular tissues was evidenced by the histopathological data highlighting the damage of interstitial tissue, showing a decrease in the number of seminiferous tubules with mild spermatogenesis hypoplasia when compared with that in the control group [67].

Flaxseed

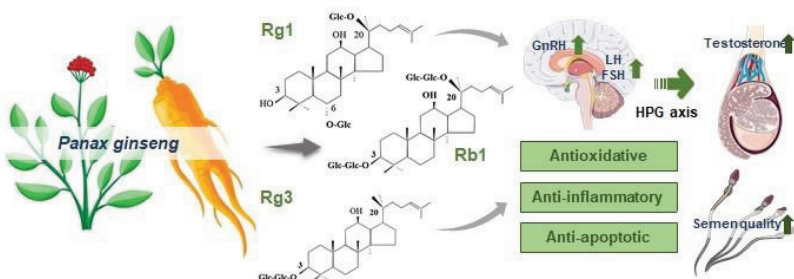
Flaxseed contains multiple metabolic components but its main component is oil containing linseed oil [36%], protein [24%], and fiber [32%]. Flaxseed is one of the rich herbal sources of the n-3 fatty acid, α -linolenic acid (ALA), and secoisolariciresinol diglycoside (SDG). Feeding male rats, with 5% dietary flaxseed decreased the weight of all prostate lobes, while 10% dietary flaxseed enhanced serum testosterone and estradiol levels and produced higher relative weights of the accessory sex gland, all prostate lobes, the seminal vesicle, and the testes [68]. Another study showed that flaxseed dietary at doses of 13%, 20%, 26% 40%, was not able to increase the diameter of the seminiferous tubules compared to the control group, suggesting that flaxseed dietary did not have adverse effect on spermatogenesis or testis [69]. Another study on rats, showed that exposure to flaxseed/flax meal prenatally and/or postnatally decreased the prostate weight, as well as increased the serum LH and cauda epididymal sperm counts in the rat [70]. Tou et al `suggested that it is important to establish the age of exposure and dose of flaxseed that will provide the most health benefits with the fewest risks [70].

Ginseng

Ginseng (*Panax*) is one of the most consumed medicinal plants. Ginseng roots contain different pharmaceutical constituents ginsenosides (saponins), polyacetylenes, polyphenolic compounds and acidic polysaccharides, and among the constituents, ginsenosides are the most pharmaceutically active. Until now, 38 ginsenosides have been separated from ginseng roots, with five main ginsenosides (ginsenosides Rb1, Rb2, Rc, Re and Rg1) which are more than 80% of the total ginsenosides [71]. Flavonoids, the main group of total phenolic constituents, are found in greater concentration in the ginseng [72]. This plant has different effects like protecting muscle from exercise induced by oxidative stress,

improving erectile parameters such as penile rigidity, girth, erection duration, libido and patient satisfaction [73]. Ginseng causes a significant decrease in total chromosomal aberrations, sperm abnormalities and increase in testosterone concentration and sperm numbers and motility [71, 74]. Ginseng has a protective effect against Zearalenone (ZEN) which disturbs the testicular function [71]. Kumar et al and Kang et al, reported that ginseng extract protect the testis by decreasing the activity of testicular acid phosphatase, LPO level and significantly increasing the alkaline phosphatase activity. Their protective effect may be due to the higher ability to eliminate free radicals and protect the cell membranes from the lipid peroxidation and their effect on endocrine system as well as the antagonistic effects on ZEN [71, 74]. Ginseng has protective and therapeutic effects on testicular damage induced by ZEN, proving that ginseng might be a useful agent in preventing and treating testicular damage induced by environmental pollutants [71]. Hwang et al, indicated that ginseng improves the survival rate and sperm quality in guinea pigs exposed to 2, 3, 7, 8-tetrachlorodibenzopdioxin (TCDD) and stimulates the spermatogenesis [75]. Ginseng could be a useful agent to protect the toxic effects, especially testicular, of an endocrine disrupter [75]. In another study, the epididymal sperm count was increased significantly in the Panax ginseng (PG) -treated group for 56 days, compared with the control group. PG increased glial cell-derived neurotrophic factor (GDNF) Messenger Ribonucleic Acid (mRNA) and protein expression in rats by 24.1% and 25.2%, respectively. These results show the probable association of elevated GDNF level and spermatogenesis. Panax ginseng has an effect on spermatogenesis via the induction of GDNF expression. It has been reported that ginseng reduces the side effects of cytostatic chemotherapeutics, such as 5-fluorouracil, mitomycin C, vinblastine, and cyclophosphamide [73]. The ginseng extract could give

effective protection against radiation-induced testicular damages. Administration of ginseng before gamma radiation treatment significantly protected the germ cell population against the gamma radiation in mice [74]. Salvati et al, also showed that sperm viability, plasma testosterone, FSH, and LH levels in 30 oligoasthenospermic patients were increased by treatment with *P. ginseng* extract. Ginseng intestinal metabolite-I (GIMI) was found to be a potential candidate as an additive to chemotherapeutic agents that are toxic to testes and GIMI can effectively prevent the testicular toxicity induced by doxorubicin [76]. In another study, it was found that the sperm count in the testes and epididymides of the male rats treated with the tissue-cultured root of wild *Panax ginseng* (tcwPG) powder was significantly higher than the control group. These spermatogenic effects of tcwPG might be associated with the combined effect of its many constituents like ginsenosides, polyphenol and minerals [77]. In another study, it was found that rats treated with ginseng exhibited increased cAMP-responsive element modulator (CREM) mRNA and CREM protein expression. These results indicate that ginseng may improve the motility and total number of sperm, probably through CREM activation, with no severe side effects [78].



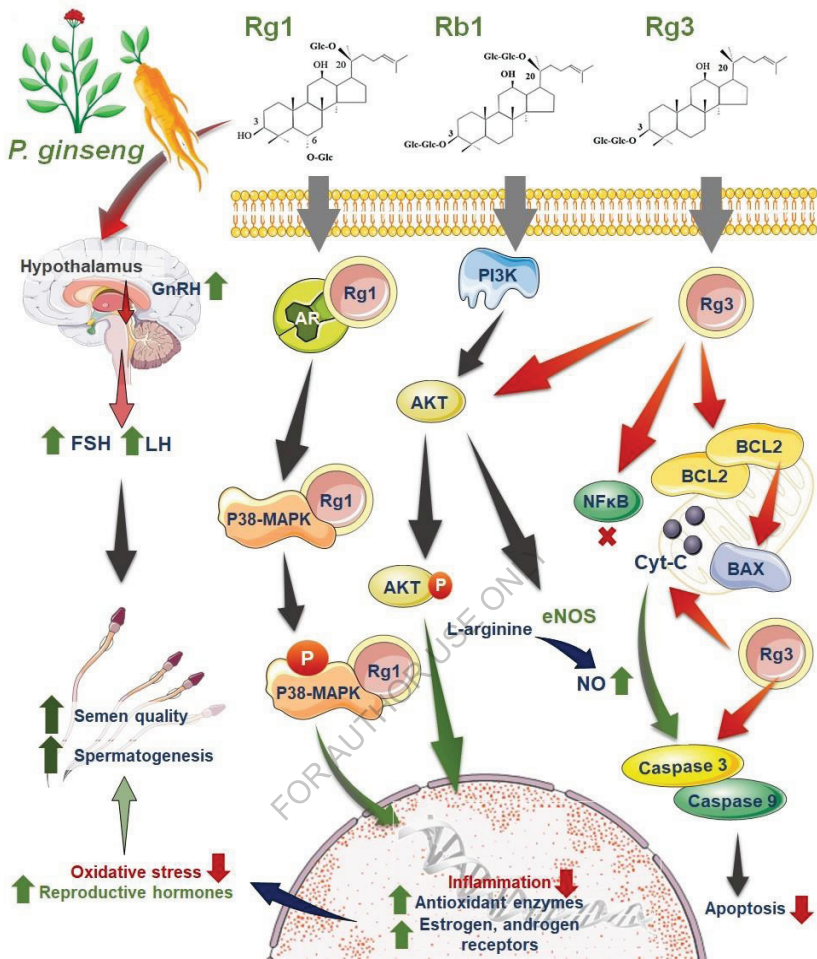


Figure 1. Mechanism of actions of ginsenosides (Rb1, Rg1, and Rg3) on male reproductive functions.

Parsley

Parsley (*Petroselinum crispum*) is a member of the Umbelliferae family that has been used in the food, pharmaceutical, perfume, and cosmetics industries. Parsley has various therapeutic effect such as antianemic, antihyperlipidemic, menorrhagic, antioxidant, antimicrobial, anticoagulant, antihep-atotoxic and laxative [71]. Flavonoids, the major group of total phenolic compounds, are found in parsley which either scavenge free radicals or increase the production of GST [72]. It is indicated that parsley oil contain flavonoids (apiin, luteolin-, apigenin-glycosides) , essential oil (apiol, miriszticin) , cumarines, (bergapten, imperatorin) and vitamin C. The protective effect of parsley oil might be due to the higher content of these flavonoids in parsley. It has been indicated that treatment with parsley oil increases the levels of glutathione reductase and SOD activity [71].

Lepidium Meyenii (Maca)

Lepidium meyenii, a traditional Peruvian cruciferous vegetable known as Maca used in the distant past, belongs to the Brassicaceae family. The hypocotyl, the comestible part of the plant, can increase sperm production [79]. Traditionally, the dried hypocotyls of Maca are boiled and used as juice [80]. The root of the Maca has biological effect. Dry Maca hypocotyls have 59% carbohydrates, 10.2% proteins, 8.5% fiber, 2.2% lipids and a number of other compounds, including most of the essential amino acids Arginine, a constituent of Maca, that has been proven to have good effect on male fertility. Maca also contains sterols, such as campesterol, stigma sterol and β -sitosterol. However β -sitosterol has an antifertility effect in male rats rather than a compound that increases fertility. β -Carbolines inhibit apoptosis and improves spermatogenesis

[81]. Piacente et al, found that Maca also contained (1R, 3S) -1-methyltetrahydroβcarboline-3 carboxylic acid [82]. Maca has been found to have antioxidant properties in vitro and in vivo [80]. The first evidence of improvement effect of Maca in spermatogenesis was reported in male rats by oral administration of an aqueous extract from the roots of *Lepidium meyenii* (Maca) in dose of 666•6 mg/day for 14 days to normal adult male rats by acting on first mitosis (stages IX–XI) [83]. Gonzales et al, demonstrated that Maca also increases the sperm number and motility in normal men without changing serum level of testosterone, LH and FSH [81]. Studies suggest that using Maca at doses of 1•5-3•0 g, is enough to improve the sexual desire, and does not affect the production and/or catabolism of testosterone [84]. Maca (2 g/kg BW) prevented the deleterious effect of administration of Malathion (80 mg/kg) on spermatogenesis in mice. Also, *L. meyenii* may become in a potential treatment of male infertility due to lead exposure. Maca reversed the effects of lead acetate (LA) administration on spermatogenesis by protecting onset of mitosis (stages IX–XI) and spermiation (stage VIII) [80].

Pumpkin

Pumpkin (*Cucurbita pepo* L.) seed and seed oil have macro- and micro compounds. The protein level is high in seeds [25–51%] [85] and in seed oil [40% to 60%]. The seed oil contains fatty acids oleic (up to 46.9%) , linolenic (up to 40.5%) , palmitic and stearic up to 17.4%. There are 1% phytosterols presented in free and bound forms; squalene; chlorophyll pigments, 4–5% minerals including selenium, calcium, copper, iron, manganese, phosphorous, potassium, and zinc, which is necessary in male reproductive system; approximately 30% pectins [86]. Pumpkin seeds improve libido and semen quality by elevating the serum

testosterone level [87, 88]. It has been demonstrated that pumpkin seeds and daily rich diet of zinc can decrease the undesirable side effect of lead contaminants and improve the sexual health status [85]. Also, pumpkin seed can inhibit citral induced hyperplasia of the ventral prostate lobe by reducing protein binding prostate levels (PBP), weight of ventral prostate lobe and improve histology of testis. Therefore, it may be helpful in the management of benign prostatic hyperplasia [3]. Pumpkin seeds improve sexual stimulation and intromission and ejaculatory latency [89]. Pumpkin causes a significant reduction in sperm count with primary and secondary abnormalities by producing further zinc and protein. Therefore, Pumpkin is proposed for both the prevention and treatment of infertility in male animals [4]. Fluted pumpkin seed oil (FPSO) has been reported have some essential components (vitamin A, tannins, linoleic acid, oleic acid and alkaloids) which suppress lipid per oxidation, improve testicular function, enhance fertility, and improve sperm count and testicular histology. FPSO improves semen parameters and has little or no effect on testicular histology when administered at a low dose of 400 mg/kg body weight [75]. Tannins are classified as antioxidants, at a high dose and could become pro-oxidant by increasing lipid per oxidation [90]. This explains for the drop in sperm count and motility including hormonal levels at a high dose of 800 mg/kg body weight FPSO [75]. Also, the findings of our study indicated that pumpkin seed extract could recover the side effects of CP the epididymis histology and sperm parameters through preventing oxidative stress [91].

Sesame

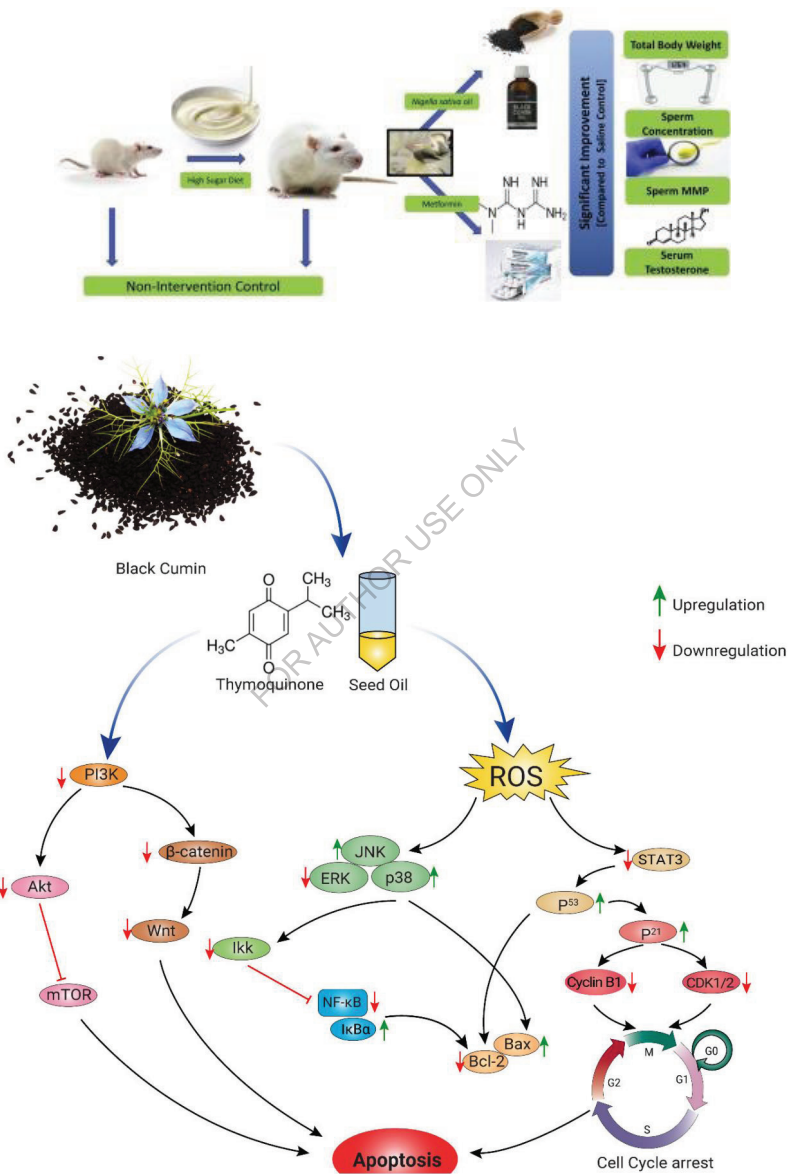
Phytochemically, sesame (*Sesame indicum*) has phenolic compounds (phenols, sterol, lignans and flavonoids) , non-protein amino acids, cacogenics glycosides, alkaloids, polyunsaturated fats and lipids,

mucilage, phospholipids, thiazole, pyrroles, disulphide, ketones, aldehyde, vitamins (B1, B2, C and E) [92] and trace elements/minerals such as calcium, iron, magnesium, zinc, copper and phosphorus [93]. Sesame contains abundant lignans such as lipid-soluble lignans (sesamin and sesamol), sterol and water-soluble lignan glycosides (sesaminol triglucoside and sesaminol diglucoside) with diverse antioxidative properties, has the ability of improving fertility potential of the male reproductive system. All parts of the plant are useful [94, 95]. Sesame improves epididymal sperm reserved with larger spermatocytes in a dose-dependent manner. Sesame can also increase body weight in a dose-dependent manner. Sesame could increase testosterone level and decrease FSH level. Sesame has positive effects on the storage capacity for the sperm in the epididymis in a dose-dependent manner [95]. We recently showed that sesame seed could improve testicular parameters, fertility, spermcount and motility, and also it may increase the LH. However, a diet containing sesame seed did not effect on epididymal tissue and body weight [96, 97]. Sesame improves sperm motility and morphology due to the reactive oxygen species [93] and free radical scavenging moiety of sesame lignans as a powerful anti-oxidant with inhibitory effect on lipid peroxidases, dismutase and carnitine oxidase, which inhibit sperm motility and maturation in the epididymis [98]. Sesame lignans has positive effect on the male reproductive tract because of binding to the estrogen receptors (ER) more especially the ER than the ERb. In addition, it modulates the activity of the androgen receptor (AR) in the testis, influences the hypothalamic pituitary –testicular pathway [99]. Sesame can also increase the diameter of the seminiferous tubules in a dose-dependent manner [95].

Nigella sativa

Nigella sativa (*N. sativa*) is known as black seed, belongs to the family of Ranunculaceae. It has been used in many Middle Eastern countries as a natural medicine [100]. *N. sativa* seeds contain nutritional components such as carbohydrates (monosaccharides in the form of glucose, rhamnose, xylose, and arabinose), fats, vitamins, mineral elements, and proteins, including eight of essential amino acids [101, 102]. *N. sativa* seeds 11 November 2013, Volume 10, Number 4 have much unsaturated (linoleic and oleic acid) and essential fatty acids [103]. The seeds contain carotene calcium, iron, and potassium. *N. sativa* increases fertility, weight of reproductive organs, numbers of mature Leydig cells in male albino rats due to increasing androgen level. Also, it can increase sperm motility of cauda epididymis by affecting the activity of enzymes of oxidative phosphorylation [102]. The fixed oil of *N. sativa* oil consists of 50% linoleic acid, 25% oleic acid, 12% palmitic acid, 2.84% stearic acid, 0.34% linolenic acid and 0.35% myristic acid [104]. High performance chromatographic analysis of *N. sativa* oil showed many compounds like thymoquinone, dithymoquinone, thymohydroquinone and thymol [103]. *N. sativa* oil has been reported to have antioxidant properties [105]. Decreasing serum lipid level by *N. sativa* oil may be due to the hypolipidemic effects of oleic, linoleic acids [106] and major unsaturated fatty acids of the oil or from its effect on lipoprotein. Supplementation of animal diets with oils rich in polyunsaturated fatty acids, such as linoleic acid has positively influenced reproductive system [105]. In another study, results revealed that *N. sativa* oil could improve reproductive efficiency, seminal vesicle weight, testosterone level, sperm motility and sperm quality in hyper-cholesterolemic rats. The improving

action of *N. satativa* in the fertility index may be due to its antioxidative and hypolipidemic effects [106].



Crocus sativus

Crocus sativus L is a perpetual stemless plant of the Iridaceae family, which is known as saffron. This plant is widely tilled in Iran and other countries, including India and Greece. Crocus sativus compounds have medicinal activity and important volatile agents (e.g., safranal), bitter principles (e.g., picrocrocin) and dye materials (e.g., crocetin and its glycoside, crocin) [107]. Saffron's extract has various compounds like á-Krustyn, crocins including the crocin, tricrocin, pykrvkrvsyn and safranal. The interested segment of saffron is its stigma [108, 109]. Saffron and its constituents such as safranal and crocins decrease free radicals in vitro experiments [110]. In traditional medicine, saffron has been used with various applications such as sexual potential stimulant [111]. Saffron improves rigiscan parameters (rigidity and tumescence) and sexual functions such as erectile function, sexual satisfaction, orgasm, sexual desire and overall satisfaction [112]. Modaresi et al. demonstrated that saffron increases FSH, LH and testosterone serum levels in mice by consumption of 100 mg/kg dosage during 20 days [108]. In another study, it was reported that consumption of 200mg/kg of saffron has inhibitory and toxic effects on testicle' tissue and spermatogenesiswhile low dosage (50-100mg/kg) stimulates insignificantly the testicle tissue and spermatogenesis procedure [10]. It seems that the 100 mg/kg/48h concentration of saffron has the most impact [108, 109]. Another study showed that Crocin, at all doses (100,200,400 mg/kg body wt) and aqueous crude extract of C. sativus, especially at doses of 160 and 320 mg/kg body wt., increases mounting frequency (MF) , intromission frequency (IF) , erection frequency (EF) , behaviors and reduces mount latency, intromission latency (IL) and ejaculation latency (EL) parameters in rats [107].

Dactylorhiza maculate

Dactylorhiza maculate is highly used in India, China, Nepal, Europe and other regions of the world. The powder of its dried root-tubers is known as salep. Dactylorhiza maculate contains various compounds such as glucomannan, nitrogenous substances, starch, protein, sugar, hydroxybenzaldehyde, ferulic acid, quercetin, daucosterol, cirsilineol and steroids. The plant is also used in ice cream, soft drinks and confectionery [119]. Consumption of salep root extract increases the desire of opposite sex, number of erection and ejaculation, animal's body weight, weight of reproductive organs, sperm number and testosterone hormone and semen fructose [120]. Esteves et al, demonstrated that salep improves sexual male strength [121]. Aqueous extract of salep root (40 mg of salep extract in 200 μ l distilled water) improves spermatogenesis and the sexual organs health in male mice by increasing the testosterone and LH levels so that, it can increase Leydig cells proliferation and testosterone hormone. Salep extract effects mostly on proliferative cells (spermatogonia, spermatocyte and spermatid) and does not have effect on sertoli cells, which have lost its proliferative property.

Conclusion

In conclusion, earlier RCTs have emphasized how medicinal plants can increase male fecundity. However, additional RCTs are necessary to confirm the aforementioned effects, establish the maximum dosage and duration of treatment with herbal remedies, and assess any possible adverse effects of such therapies to create a novel strategy for the treatment of male infertility. Complex processes govern how the endocrine system controls male reproductive functions. Testicular hormones are susceptible to positive and negative feedback controls on the main endocrine axis controlling male reproduction, the HPG axis, as well as modulation by a variety of other endocrine axes and a variety of other reproductive and non-reproductive hormones. Male subfertility or infertility can be brought on by quantitative or qualitative flaws in any of these hormonal interactions or their receptors, which can result in hyper- and hypogonadotropic hypogonadisms, excess androgen and estrogen, and hyperprolactinemia. The precise knowledge of endocrine disruptions' role in male infertility could open new avenues for investigation and the development of diagnostic tools, management strategies, and therapeutic regimens for this complex and delicate pathological condition. In this paper, a critical review of the effects of various plants with applications for treating and preventing male infertility has been provided. The majority of plant extracts contain phenolic compounds (phenols, sterol, lignans, and flavonoids), vitamins (B1, B2, B3, and C), folic acid, bio-trace elements (Ca, Mg, P, Zn, K, Cu, and Fe), and the majority of the essential amino acids, volatile oils, polyphenols, and saponins, among other major bioactive components. Numerous phyto-medicines are beneficial for spermatogenesis, sperm parameters (sperm motility, count, viability), increasing Leydig cell counts, seminiferous tubule diameters,

reducing abnormal sperm, improving histopathological recovery, sexual stimulation (erection, intromission, and ejaculatory latency), and increasing concentration and motility of sperm in ejaculation volume. Suitable methods to enhance the efficacy of therapeutic plants' reproductive system consist of Superoxide dismutase and other antioxidant enzymes that can be increased by their anti-oxidant actions. Alkaline phosphatase activity, catalase, glutathione peroxidase, peroxidase activity, and (SOD), function as a defense mechanism against reactive oxygen species and can efficiently scavenge free radicals. Androgenic activity: This refers to the ability to raise free testosterone levels to improve male sexual ability. It has been demonstrated that testosterone, particularly its active converted form, dihydrotestosterone, stimulates erection by keeping the amount of nitric oxide stable. -The impact of plant compounds on LH, FSH, and GnRH: Hormone levels for estrogen, progesterone, pregnenolone, FSH, and LH are modulated by medicinal plants. In actuality, estrogens are crucial to the control of masculine Reduce lipid peroxidation products (TBARS), ROS, OS, malondialdehyde levels (MDA), and sexual function. Reactive oxygen species are produced by an established mechanism called iron-induced lipid peroxidation. Numerous plant extracts that are not poisonous can inhibit lipid peroxidation brought on by Fe²⁺. Plant products may contribute to the relaxation of the cavernous muscle and, consequently, erection by inhibiting phosphodiesterases, promoting the synthesis and release of nitric oxide (NO), or stimulating nitric oxide synthase. CAMP-responsive element modulator (CREM) mRNA and protein levels should be increased. That might increase sperm movement and quantity overall. Although the general public assumes that herbal remedies are safe, some studies reveal that an incorrect dosage can also have some negative effects. For this reason, a lot of studies has been devoted to creating new

drugs from herbal remedies, which have a variety of useful properties. Spermatogenesis is an active process. A dependent procedure that requires an ideal intake of flavonoids, minerals, vitamins, and antioxidants. Numerous dietary approaches have been suggested to improve sperm quantity, motility, and viability in the long run. Phytomedicines are still used to treat male infertility for several reasons, including enhancing natural fertility through their effects on various male reproductive systems and enhancing sperm parameters for cutting-edge reproductive technologies. To treat male infertility, doctors must have some understanding of the helpful medicinal plants based on scientific research. This knowledge will allow them to combine medicinal plants with contemporary medications.

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