Effects of Herbal Medicine on Male Infertility

Forouzan Mohammadi[1] , Hossein Nikzad[1]*, Aliakbar Taherian[2] , Javad Amini Mahabadi[1] , Mahdi Salehi[2]

1. Gametogenesis Research Center, Kashan University of Medical Sciences, Kashan- Iran.
2. Anatomical Sciences Research Center, Kashan University of Medical Sciences, Kashan, Iran.

Dr. Hosein Nikzad is an academic member (Professor) in Kashan University of Medical Sciences and teach anatomy and embryology courses for medical and paramedical students for 20 years. His interest research field is clinical emberyoloy, Ivf, reproduction and androloy. Until now, he published more than 40 manuscripts at the national and international journals. Now, he is head of gametogenesis research center in Kashan University of Medical Sciences.

Article info:
Received: 7 Jun 2013
Accepted: 25 Aug 2013

Key Words:
Male Infertility,
Herbal Medicine,
Reproductive System,
Sperm

ABSTRACT

The inability to have a child is a baleful event for millions of couples in their life, and a large percentage of them have a personal frustration. The problem of infertility in couples is distributed equitably between the two sexes. Among different methods, medicinal plants have been used in many Nations to treat male infertility problems. These medicinal herbs are used to treat sperm disorders, dysfunctioning of the libido, 2 sexual asthenia and erection. Herbs provide a therapeutic option, which is affordable and available for infertile couples, and herbalism is the main form of treatment in our health system. So in this review, we have summarized most of the data dealing with the positive effects of plant extracts on mammalian reproductive system.

1. 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 forms of infertility problems which 40% of these problems are due to male factor [2, 3]. Reproductive ability in the male contain the production of semen containing normal spermatozoa (quality) in the 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 treatment like surgery, chemicals and herbal drugs and laboratory methods are available to help fertility. According to several studies, a number of botanical medicines have a positive effect on sperm parameters [6]. Herbal plants has been famous from ancient times among people and in recent years, a multilateral approach has been appeared on using herbal medicines along with 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 paper is to critically review the available literature on herbal

*** Corresponding Author:**
Hossein Nikzad, PhD
Address: Gametogenesis Research Center, Kashan University of Medical Sciences, Kashan- Iran
Tel/Fax:: +98 (31) 55621158
E-mail:nikzad_h@kaums.ac.ir

medicines and their possible roles in treatment of male infertility.

2. Materials & Methods

We searched in Google scholar, Science direct and Pubmed for different types of plants, which have effect on fertility process using their scientific names. Then we chose the plants that have positive effect on fertility and searched articles with different key words such as "the effect of (name of plant) on the reproductive system or reproductive function or spermatogenesis in the male". We chose original papers that have been published from 1990 to 2012 After downloading PDF files, we studied all of the articles. Information from selected articles was classified according to the target effect of a plant extract on male reproductive function and to the subject (rodent, human) used to assess the potential activity of a plant extract.

3. Results & Discussion

Tea

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, group of catechins that includes catechin, epicatechin, gallocatechin, epigallocatechin, catechin gallate, epicatechin gallate, gallocatechin 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 [9]. The current researches have shown that both green and black tea contain flavenoids such as quercetin, kaempferol and myricetin, which have strong anti-toxic and anti-carcinogenic properties. Green tea extract (GTE) had inhibitory effect on cadmium (Cd) toxicity by decreasing the formation of lipid peroxidation products [10] level, and minimal histological changes in the testes of rats which were treated with Cd + GTE. Catechin normalizes lipid peroxidation in Cd – poisoned rats testes [11]. 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 testes of male rats since it could decreased carbon tetrachloride (CCl4-) induced lipid peroxidation [12].

Another study showed that both fermented rooibos and green tea significantly increased the superoxide dismutase (SOD) activity in the tissue of testis, also they 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 and can reduce free radicals effectively and decrease the damage of spermatogenic cells [13]. It has been reported that catalase, SOD, peroxidase activity (POD) and glutathione peroxidase (GSH-Px) act as a defense system against reactive oxygen species [14]. These results suggest that fermented rooibos and green tea can be used as a supportive therapy for male infertility, in cases where oxidative stress is involved [15].

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 [16]. In another study onhumans, 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 [17]. 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 [18].

Carrot

Daucus carota commonly known as "Carrot" belongs to the family of Apiaceaeis, 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 [19]. The extract of carrot seed has more antioxidants and can increase the sperm reserves in cauda epididymis (CESR) [20]. In addition, co-administration of this extract with gentamicin can counterbalance the negative effect of gentamicin on the sperm count demonstrated in studies [19, 21]. 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 [19]. 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 [19].

Garlic

Garlic (Allium sativum) has been used as a medicine world-wide since ancient times [22]. Diallyl tetrasulphide is the bioactive organosulphur component of garlic, which have antioxidant effects [23]. 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 [24]. Some studies have reported that garlic harmsthe function of testes and has spermicidal effects on spermatozoa but some others demonstrated the opposite effect [25]. 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 [25]. Yuriko et al demonstrated that the increased concentration of testicular testosterone after feeding rats with 8 g of garlic powder was due toan increase in luteinizing hormone (LH) level in plasma. Indeed, crude garlic and garlic powder may have the same active compounds [26]. Rats fed with garlic water extract over 3 months showed an increase in epididymis spermatozoa [27]. Dixit and Joshi reported a spermatogenesis stop at the primary spermatocyte stage with 50 mg of oral administration of garlic powder for 70 days [28]. Ola-Mudathir et al. indicated that aqueous extracts of garlic caused an increase in the catalase [29] activity and protects the testis and spermatozoa against cadmium toxicity [23]. Some of these different results might be due to the type of preparations used like garlic powder [26, 28] , water extract [27] , aged garlic, raw garlic juice and heated garlic juice [30] 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 panthotenic acid, gingerol, sesquiterpene, vitamin B3 and B6 volatile oils andbiotrace elements [Ca, Mg, P and K] [31]. All major active ingredients of Z. officinale, such as Zingerone, Gingerdiol, Zingibrene, gingerols and shogaols, have antioxidant properties [32]. 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 [33, 34]. This plant has been considered as a safe herbal medicine with few side effects [35]. Both antioxidative and androgenic activity of Z. officinale have been reported in animal models [36]. 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 [29] and glutathione peroxidase (GSH) in the rat testes [31]. 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 malonhydialdehyde levels [37]. Ginger has been previously shown to stimulate spermatogenesis [31]. It was also observed that the administration of ginger can significantly increase testosterone level in plasma [38]. Co-administration of ginger and arsenite restored the reproductive organ which might be due to the androgenic activity of ginger [31]. 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 conquest 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 [39]. 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 [36].

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 [40].

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 [37].

Amin et al showed that Z. officinale could increase the activities of testicular antioxidant enzymes and restore

sperm motility of cisplatin-treated rats beside protection against cisplatin-induced testicular damage [41]. 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 [42].

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 [43]. 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 activityalmost equal to a-tocopherol, which was used as a reference [44]. 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 [43].

Capsaicin

Capsaicin (CAP 8-methyl-N-vanillyl-6-nonandamide) 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 [45].

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 [46]. 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 [47]. P. longum-treated mice showed a significant increase in the weight of testes, cauda epididymis dies 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 [46].

Cinnamomum

Cinnamomum (family of Lauraceae) species contain volatile oils, tannins, terpenoids, mucilage, oxalates and starch. Different chemical constituents of C.zeylanicumare known to have significant germicidal, antiulcerogenic andcytotoxic effects. In a study, the extract of Cinnamomum increased the weight of testes, caudae epididymidies 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 [48].

In another study, oral administration of C.zeylanicumextract 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 [49].

Fenugreek

Fenugreek (Trigonella foenum-graecum) is a herb belonging to the family of leguminosa [50] 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 [51]. 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 [50]. It has been reported that the polyphenolic extract of fenugreek seeds has an antioxidation effect in vitro [52]. 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 [53].

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, a-linolenic acid (ALA) , and secoisolaricires in oldiglycoside (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 [54]. 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 [55]. 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 [56]. 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 [56].

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 [57]. Flavonoids, the main group of total phenolic constituents, are found in greater concentration in the ginseng [58]. 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 [59]. Ginseng causes a significant decrease in total chromosomal aberrations, sperm abnormalities and increase in testosterone concentration and sperm numbers and motility [57, 60]. Ginseng has a protective effect against Zearalenone (ZEN) which disturbs the testicular function [57]. Kumar et aland 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 [57, 60]. 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 [57]. 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 [61]. Ginseng could be a useful agent to protect the toxic effects, especially testicular, of an endocrine disrupter [62]. 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 ginsenghas 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 [59]. 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 [60]. 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 (GIM-I) was found to be a potential candidate as an additive to chemotherapeutic agents that are toxic to testes and GIM-I

can effectively prevent the testicular toxicity induced by doxorubicin [63].

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 [64].

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 [65].

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 [57]. Flavonoids, the major group of total phenolic compounds, are found in parsley which either scavenge free radicals or increase the production of GST [58]. 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 [57].

Lepidium Meyenii (Maca)

Lepidium meyenii, a traditional Peruvian cruciferous vegetableknown as Maca used in the distant past, belongs to the Brassicaceae family. The hypocotyl, the comestible part of the plant, can increase sperm production [66]. Traditionally, the dried hypocotyls of Maca are boiled and used as juice [67]. 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 [68]. Piacente et al, found that Maca also contained (1R, 3S) -1-methyltetrahydroβ-carboline-3 carboxylic acid [69]. Maca has been found to have antioxidant properties in vitro and in vivo [67]. 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) [70]. 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 [68]. 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 [71]. Maca (2 g/kg BW) prevented the deleterious effect of administration of Malathion (80 mg/kg) on spermatogenesis in mice. Also,L. meyenimay 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 (stageVIII) [67].

Pumpkin

Pumpkin (Cucurbita pepo L.) seed and seed oil have macro- and micro compounds. The protein level is high in seeds [25–51%] [72] 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 [73]. Pumpkin seeds improve libido and semen quality by elevating the serum testosterone level [74, 75]. 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 [72]. 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 [76]. 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 [62]. Tannins are classified as antioxidants, at a high dose and could become pro-oxidant by increasing lipid per oxidation [77]. This explains for the drop in sperm count and motility including hormonal levels at a high dose of 800 mg/kg body weight FPSO [62]. 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 [78].

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) [79] and trace elements/minerals such as calcium, iron, magnesium, zinc, copper and phosphorus [80]. Sesame contains abundant lignans such as lipid-soluble lignans (sesamin and sesamolin) , 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 [81, 82]. 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 [82].

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 affect on epididymal tissue and body weight [83, 84].

Sesame improves sperm motility and morphology due to the reactive oxygen species [67] and free radical scavenging moiety of sesame lignans as a powerful anti oxidant with inhibitory effect on lipid perioxidases, dismutase and carnitine oxidase, which inhibit sperm motility and maturation in the epididymis [85]. 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 [86]. Sesame can also increase the diameter of the seminiferous tubules in a dose-dependent manner [82].

Allium cepa

Allium cepa (onion) has antioxidative andandrogenic effects, and also can promote spermatogenesis cycle [87]. Onion has phytochemicals and micro constituents such as vitamins, flavonoids, trace elements, fructans, and sulphur compounds, which may have a positive effects against free radicals [24]. S-Methylcysteine sulphoxide is bioactive organosulphur components of onion which have antioxidant properties [23]. Also, onion is a quercetin-rich vegetable [88] , which decreases abnormal sperm and number of stained Sertoli cells and alleviate male reproductive toxicity induced by Diesel Exhaust Particles (DEPs) with the dose of < 0.1% and increases the testis weight. In the high-dose quercetin group, DSP) decreased daily sperm production (and Sertoli cell are decreased, but the incidence of morphologically abnormal sperm is increased [89]. Ola-Mudathir et al, reported that administration of onion extract protects the testis and spermatozoa against Cadmium (Cd) toxicity due to the reduction of the level of LPO and increasing the levels of GSH, SOD and CAT in the testis and reduction of GST activity [23]. Khaki et al. demonstrated that administration of onion juice (1 g/rat/day) for 20days increases sperm count, viability, and motility. The onion fresh juice can significantly increase the recovery of sperm health parameters, such as count, motility and serum total testosterone and total anti oxidants capacity [90] levels in T. gondii- infected rats [24].

Apium graveolens

Apium graveolens L. (AG) [celery, family: Umbelliferae] ,is commonly used as a spice with medicinal properties. Phytochemical investigations of AG seeds revealed the presence of terpenes such as limonene, flavonoids like apigenin and phthalide glycosides [91]. One study demonstrated that treatment with AG extract significantly reduces reproductive toxicity induced by Sodium valproate (VPA) in male albino rats by normalizing sperm count, sperm motility ,and the histopathological recovery. The extract of crude AG has protective

properties in rats against intoxication with paracetamol, thioacetamide and CCL4 due to its antioxidant property and detoxification capacity [92].

Artemisia annuaL

Artemisia annuaL. also known as sweet wormwood, annual wormwood or sweet Annie isan aromatic annual plant which is the source of essential oils and artemisinin [93]. A. annuaL. increases the proliferation of spermatogenic cell lines; transformation from primodial cells to spermatids and further to spermatozoa at a high rate. Also, it enlarges central lumen of the seminiferous tubules. A. annuaL. increases vascularity of interstitial and the number of leydig cells, which secrete testosterone, due to the increasing spermatogenic activity. Ajah and Eteng reported that intraperitoneal administration of gradedsingle acute doses of A. annuaL. induced adverse histological changes on the ovaries which may predispose to infertility, but the testes were not affected and retained their normal architectureand normal spermatogenic activity [94].

Tribulus Terrestris

Tribulus terrestris [family: Zygophyllaceae] , is a flowering plant. It is about 30 to 70cm high; it grows annually in summer, has pinnately compound leaves and stellate shaped fruits [95]. Studies show that Tribulus terrestris contains steroids, saponins,essence, flavonoids, alkaloids, unsaturated fatty acids, vitamins, tannins, resins, nitrate potassium, aspartic acid and glutamic acid [96]. Tribestan is presented in Tribulus terrestris increases libido and prevents reluctance, infertility and menopausal disorders. Dioscin is a component of Tribulus terrestris that increases male sexual ability by increasing free testosterone levels and modulating estrogen, progesterone and pregnenolone levels [96]. Saponins and protodioscin (estradiol glycosides) increases the levels of testosterone and LH, which are presented in Tribulus terrestris. Because of these effects, this plant has been used for the treatment of sexual and erectile dysfunctions in the traditional medicines [97, 98] , also this plant increases androgen and sexual desires [99] , blood pressure of penile artery [100] ,the mean number of the primary spermatocytes in the dose of 10 mg/kg [101]. Studies have shown that alcoholic extract of a plant in the family of Tribulus terrestris with the dose of 50 mg/kg could significantly increase free testosterone level in body [99]. Another study done on sheep, showed that using 1.5 grams of Tribulus terrestris extract for 40 days increased spermatogenesis in sheep during breeding season [96]. Studies show that Tribulus terrestris extract can improve erection and sexual behavior in rat and increase sexual hormones in rat, rabbit and primate [97, 100]. The studies show that Tribulus terrestris plant increases secretion of LH from pituitary gland by containing saponins. LH stimulates the production of testosterone and increases sperm production, libido and improves erectile function [96]. Furostanol is one of the saponins in Tribulus terrestris stimulates spermatogenesis and improves the quality and quantity of sperm [96]. Tribulus terrestris increases the thicknesses of wall of seminiferous tubules and increases leydig cells and the weight of testes and body [102] , the average diameter of seminiferous tubules and stimulates germinative and endocrine functions of the testes producing its precocious development [1]. Tribulus terrestris (protodioscin) treatment lead to an invariable increase in spermatozoa concentration in humans to approximately 160% [1]. Bashir et al,reported that administration of Tribulus terrestris significantly increases the number of germ cells in the testes of adult rats [1]. Tribulus terrestris extract has a positive effect on the quality and quantity of sperm, increases ejaculation volume and spermatozoides motility in birds [96].

Urtica dioica

Urtica dioica is known as stinging nettle, grows in many countries such as Iran, Greece and Turkey [103]. Mavi et al. reported that U. dioica contains phenolic compounds, especially flavonoids [104]. Flavonoids generally have antioxidant properties.Golalipour et al. reported that administration of hydroalcoholic extract of U. dioicaleaves (100mg/ kg/ day IP for the first5 days before induction of diabetes) preserves seminiferous tubules activity in streptozotocin-induced diabetic rats and can increase seminiferous tubular diameter (STD) and seminiferous epithelial height (SEH) ; however, the mechanism of exact is not clear [103]. But in another study,the Intraperitoneal injection (IP) of the hydroalcoholic extract of Urtica dioica leaves (100mg/kg/day) for 28 days, after streptozotocin-induced diabetic, had no beneficial treatment effect against histomorphometric alterations in seminiferous tubules of rats [105].

Nigella stativa

Nigella stativa (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 [106]. N. satatiiva 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 [107, 108]. N.satativa seeds

have much unsaturated (linoleic and oleic acid) and essential fatty acids [109]. The seeds contain carotene calcium, iron, and potassium. N. satativa 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 [108]. The fixed oil of N. satativa oil consists of 50% linoleic acid, 25% oleic acid, 12% palmiticacid, 2.84% stearic acid, 0.34% linolenic acid and 0.35% myristic acid [110]. High performance chromatographyic analysis of N. satativa oil showed many compounds like thymoquinone, dithymquinone, thymohydroquinone and thymol [109]. N. satativa oil has been reported to have antioxidant properties [111]. Decreasing serum lipid level by N. satativa oil may be due to the hypolipidemic effects of oleic, linoleic acids [112] 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 [111]. In another study, results revealed that N. satativa 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 [111].

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) [113]. 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 [114, 115]. Saffron and its constituents such as safranal and crocins decrease free radicals in vitro experiments [116]. In traditional medicine, saffron has been used with various applications such as sexual potential stimulant [117]. Saffron improves rigiscan parameters (rigidity and tumescence) and sexual functions such as erectile function, sexual satisfaction, orgasm, sexual desire and overall satisfaction [118]. 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 [114]. In another study, it was reported that consumption of 200mg/kg of saffron has inhibitory and toxic effects on testicle' tissue and spermatogenesis while 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 [114, 115]. 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 [76] , intromission latency (IL) and ejaculation latency (EL) parameters in rats [113].

Dactylorhiza maculate

Dactylorhiza maculate is highly used in India, China,Nepal, Europe and other regions of the world [2]. 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 [2]. 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 µl 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 [2].

4. Conclusion

The effects of different plants with proposed application to prevent and treat male infertility have been critically reviewed in the present article. Most plant extracts have major bioactive components including phenolic compounds (phenols, sterol, lignans and flavonoids) , vitamins (B1,B2,B3,B6,C and E) , folic acid, bio-trace elements (Ca, Mg, P, Zn, K, Cu and Fe) , most of the essential amino acids, volatile oils, polyphenols and saponins.

A number of phytomedicines have positive effects on spermatogenesis, sperm parameters (sperm motility, count, viability) , increasing Leydig cell counts, semi-

niferous tubule diameters, decreasing abnormal sperm, improving histopathological recovery, sexual stimulation (erection, intromission and ejaculatory latency) , increasing concentration and motility of sperm in ejaculation volume.

Effective mechanisms to improve the performance of the reproductive system by medicinal plants include:

-Antioxidant activities: that means they are able to increase the antioxidant enzymes,superoxide dismutase (SOD) , catalase (CAT) , glutathione peroxidase (GSH-Px) , peroxidase activity (POD) , and also alkaline phosphatase activity that acts as a defense system against reactive oxygen species and can effectively scavenge free radicals.

-Androgenic activity: that means they are able to increase male sexual ability by increasing free testosterone levels. It has been shown that testosterone and especially its active converted product, dihydrotestosterone, stimulates erection by maintaining the nitric oxide level.

-Effect of plant extracts on the levels of LH, FSH and GnRH: Medicinal plants modulate estrogen, progesterone and pregnenolone, FSH, and LH levels. Actually, estrogens play essential role in the regulation of male reproductive function.

-Decrease malonhydialdehyde levels (MDA) , lipid peroxidation products (TBARS) , ROS, OS. Iron-induced lipid peroxidation is a well-validated system for producing reactive oxygen species. Extracts of several plants can suppress Fe2+-induced lipid peroxidation and are not toxic.

-Effect of plant extracts on the relaxation of the cavernous muscle by inhibiting phosphodiesterases or stimulating the production and release of nitric oxide (NO) , or stimulating nitric oxide synthase, plants products may chip in to the relaxation of the cavernous muscle and thus erection.

-Increase cAMP-responsive element modulator (CREM) mRNA and CREM protein expression. That may improve the motility and total number of sperm.

Although public believe that herbal medicines are completely safe but some studies show that a wrong dose can have some negative effect as well. That is why much research effort has been focused on developing new drugs from herbal medicines, which have various functional features. Spermatogenesis is an energy-dependent process, which needs an optimal intake of antioxidants, minerals, vitamins,Flavonoids. Different nutritional strategies have been proposed to have a beneficial impact on sperm number, motility, and ultimately, on fertility.

In treatment of male infertility, phytomedicines are still used for several reasons including improvement of natural fertility through the effect of phytomedicines on different sections of the male reproductive system and using phytomedicines to improve sperm parameters for new reproductive technologies. It is necessary for physicians to have some knowledge about the useful medicinal plants based on scientific investigations that will give them a chance to combine medicinal plants with modern drugs to treat male infertility.

Acknowledgements

The authors gratefully acknowledge the deputy of research in Kashan University of Medical Sciences for his financial support and also all staff in the Anatomical and Gametogenesis Research Centers, Kashan University of Medical Sciences in this study.

References

1. Bashir A, Tahir M, SameeW, Munir B. Effect of tribulus terrestris on testicular development of immature albino rats. Biomedica. 2009. 25:63-68.

2. Kashani HH, Malekzadeh Shiravani S, Hoshmand F. The effect of aqueous extract of Salep prepared from root-tubers of Dactylorhiza maculate (Orchidaceae) on the testes and sexual hormones of immature male mice. Journal of Medicinal Plants Research. 2012. 6(24):4102-4106.

3. Henkel R, Maaß G, Bodeker RH, Scheibelhut C, Stalf T. Sperm function and assisted reproduction technology. Reproductive Medicine and Biology. 2005. 4(1):7-30.

4. Oyeyem M, Olukole S, Esan O. Sperm morphological studies of West African Dwarf Bucks treated with pumpkin plant (Cucurbita pepo). Int J Morphol. 2008. 26:121-126.

5. Andersen A, Jensen TK, Carlsen E, Jqrgensen N. High frequency of sub-optimal semen quality in an unselected population of young men. Human Reproduction. 2000. 15(2):366-372.

6. Sinclair S, Male infertility: nutritional and environmental considerations. Alternative medicine review: a journal of clinical therapeutic, 2000. 5(1):28.

7. Modaresi M, Mesripour M, AsadiMargh Maleki M, Hamedanian MK. The effect of saffron extract on testis tissue. Iranian journal of medicinal and aromatic plants, 2008. 24:237-243.

8. Mohajeri D, Mesgari Abbasi M, Delazar A, Doustar Y, Mousavi G. Histopathological study of subacute toxicity of Crocus sativus L.(Saffron) stigma total extract on liver

and kidney tissues in the rat. Pharmaceutical sciences. 2009. 15(2):115-124.

9. Figueiroa MS, Cesar Vieira jS, Leite DS, Filho RC, Ferreira F, et al. Green tea polyphenols inhibit testosterone production in rat Leydig cells. Asian journal of andrology. 2009. 11(3):362-370.

10. Khayatnouri M, Safavi SE, Safarmashaei S, Babazadeh D, Mikailpourardabili B. The effect of Saffron Orally Administration on Spermatogenesis Index in Rat. Advances in Environmental Biology, 2011. 5(7):1514-1521.

11. El-Shahat A, Gabr A, Meki A, Mehana E. Altered testicular morphology and oxidative stress induced by cadmium in experimental rats and protective effect of simultaneous green tea extract. Int J Morphol, 2009. 27:757-764.

12. Fadhel ZA and Amran S. Effects of black tea extract on carbon tetrachlorideâ induced lipid peroxidation in liver, kidneys, and testes of rats. Phytotherapy Research. 2002. 16(S1):28-32.

13. Awoniyi D, Aboua G, Marnewick JL, Plesis SS du, Brooks NL. Protective effects of rooibos (Aspalathus linearis), green tea (Camellia sinensis) and commercial supplements on testicular tissue of oxidative stress-induced rats. African Journal of Biotechnology. 2011. 10(75):17317-17322.

14. Khan MR, Ahmed D. Protective effects of Digera muricata (L.) Mart. on testis against oxidative stress of carbon tetrachloride in rat. Food and Chemical Toxicology, 2009. H

15. Awoniyi D, Aboua G, Marnewick JL, Plesis SS du, Brooks NL. Protective effects of rooibos (Aspalathus linearis), green tea (Camellia sinensis) and commercial supplements on testicular tissue of oxidative stress-induced rats. African Journal of Biotechnology 2011. 10(75):17317-17322.

16. Abdeen SM, Mathew TC, Dashti HM, Asfar S. Protective effects of green tea on intestinal ischemia-reperfusion injury. Nutrition. 2011. 27(5):598-603.

17. Panza VSP, Wazlawik E, Ricardo Schitz G, Comin L, Hecht KC. Consumption of green tea favorably affects oxidative stress markers in weight-trained men. Nutrition. 2008. 24(5):433-442.

18. Abshenas J, Babaei H, Zare MH, Allahbakhshi A, Sharififar F. The effects of green tea (Camellia sinensis) extract on mouse semen quality after scrotal heat stress. Veterinary Research Forum. 2011. 2(4):242-247.

19. Nouri M, Khaki A, Fathi Azad F, Rashidi MR. The Protective Effects of Carrot Seed Extract on Spermatogenesis and Cauda Epididymal Sperm Reserves in Gentamicin Treated Rats. Yakhteh Medical J. 2009. 11(3):327-33.

20. Yu LL, Zhou KK, Parry J. Antioxidant properties of cold-pressed black caraway, carrot, cranberry, and hemp seed oils. Food chemistry. 2005. 91(4):723-729.

21. Timmermans LM. Modifications in spermatogenesis following antibiotic therapy]. Acta urologica Belgica. 1989. 57(1):35.

22. Arzanlou M, Bohlooli S. Introducing of green garlic plant as a new source of allicin. Food chemistry, 2010. 120(1):179-183.

23. Ola-Mudathir KF, Suru SM, Fafunso MA, Obioha UE, Faremi TY. Protective roles of onion and garlic extracts on cadmium-induced changes in sperm characteristics and testicular oxidative damage in rats. Food and Chemical Toxicology. 2008. 46(12):3604-3611.

24. Khaki A, Farzadi L, Ahmadi S, Ghadamkheir E. Recovery of spermatogenesis by Allium cepa in Toxoplasma gondii infected rats. African Journal of Pharmacy and Pharmacology. 2011. 5(7):903-907.

25. Hammami I, Nahdi A, Mauduit C, Benahmed M, Amri,M. The inhibitory effects on adult male reproductive functions of crude garlic (Allium sativum) feeding. Asian journal of andrology. 2008. 10(4):593-601.

26. Oi Y, Imafuku M, Shishido C, Kominato Y, Nishimura S. Garlic supplementation increases testicular testosterone and decreases plasma corticosterone in rats fed a high protein diet. The Journal of nutrition. 2001. 131(8):2150-2156.

27. Challa A, Rao DR, Reddy BS. Interactive suppression of aberrant crypt foci induced by azoxymethane in rat colon by phytic acid and green tea. Carcinogenesis. 1997. 18(10):2023-2026.

28. Dixit V, Joshi S. Effects of chronic administration of garlic(Allium sativum Linn) on testicular function. Indian journal of experimental biology. New Delhi. 1983. 20(7):534-536.

29. Amara S, Abdelmelek H, Garrel C, Guiraud P, Douki T. Preventive effect of zinc against cadmium-induced oxidative stress in the rat testis. J Reprod Dev. 2008. 54(2):129-134.

30. Kasuga S, Uda N, Kyo E, Ushijima M, Morihara N. Pharmacologic activities of aged garlic extract in comparison with other garlic preparations. The Journal of nutrition. 2001. 131(3):1080S-1084S.

31. Morakinyo OA, Achema P, Adegoke O. Effect of Zingiber Officinale (Ginger) on Sodium Arseniteae"Induced Reproductive Toxicity in Male Rats. African Journal of Biomedical Research. 2010. 13(1):39-45.

32. Nassiri M, Khaki A, Ahmadi-Ashtiani HR, Rezazadeh S, Rastgar H. Effects of ginger on spermatogenesis in streptozotocin-induced diabetic rat. Journal of Medicinal Plants. 2009. 8(31):118-124.

33. Khaki A, Khaki AA, Iraj S, Bazi P, Imani SAM. Comparative Study of Aminoglycosides(Gentamicin & Streptomycin) and Fluoroquinolone (Ofloxacin) Antibiotics on Testis Tissue in Rats: Light and Transmission Electron Microscopic Study. Pak. J. Med. Sci. 2009. 25(4):624-629.

34. Grzanna R, Lindmark L, Frondoza CG. Ginger-an herbal medicinal product with broad anti-inflammatory actions. Journal of medicinal food. 2005. 8(2):125-132.

35. Dawson E, Harris WA, Teter MC, Powell LC. Effect of ascorbic acid supplementation on the sperm quality of smokers. Fertility and sterility. 1992. 58(5):1034-1039.

36. Khaki A, Fathiazad F, Nouri M, Afshin A, Hamadeh DVM. The effects of Ginger on spermatogenesis and sperm parameters of rat. Iranian Journal of Reproductive Medicine. 2009. 7(1):7-12.

37. Morakinyo A, Adeniyi O, Arikawe A. Effects of Zingiber officinale on reproductive functions in the male rat. African Journal of Biomedical Research. 2008. 11(3):329-334.

38. Anahara R, Toyama Y, Mori C. Review of the histological effects of the anti-androgen, flutamide, on mouse testis. Reproductive Toxicology. 2008. 25(2):139-143.

39. Zahedi A, Khaki A, Ahmadi Ashtiani HR, Rastegar H, Rezazadeh SH. Zingiber officinale protective effects on gentamicin,s toxicity on sperm in rats. JMP. 2010. 9(35):93-98.

40. Saeid J, Shanoon A, Marbut M. Effects of Zingiber officinale Aqueous Extract on Semen Characteristic and Some Blood Plasma, Semen Plasma Parameters in the Broilers Breeder Male. International Journal of Poultry Science. 2011. 10(8):629-633.

41. Amin A, Hamza AEA. Effects of Roselle and Ginger on cisplatin induced reproductive toxicity in rats. Asian Journal Androl. 2006. 8(5):607-612.

42. Mohammadi F, Nikzad H, Taghizadeh M, Azami-Tameh A, Hosseini M. Protective effect of Zingiber officinale extract on rat testis after cyclophosphamide treatment. Andrologia. 2013.

43. Kose E, Sarsılma M, Tas U, Kavakli A, Turk G. Rose oil inhalation protects against formaldehyde-induced Testicular damage in rats. . Andrologia. 2012. 44:342-348.

44. Wei A, Shibamoto T. Antioxidant activities and volatile constituents of various essential oils. Journal of agricultural and food chemistry. 2007. 55(5):1737-1742.

45. Sefika M, Hatice E, Aytekin O. Spermatogonial stem cell sensitivity to capsaicin: An in vitro study. 2008.6:52

46. Erdost H, Akkoc CGO, Ozfiliz N, İlhan T, Tutuncu S.The histological investigation on the testes of mice after an application of capsaicin. Veterinarski arhiv. 2009. 79(5):509-516.

47. Koul IB, Kapil A. Evaluation of the liver protective potential of piperine, an active principle of black and long peppers. Planta Med. 1993. 59(5):413-417.

48. Shah A, Al-Shareef AH, Ageel AM, Qureshi S. Toxicity studies in mice of common spices, Cinnamomum zeylanicum bark and Piper longum fruits. Plant Foods for Human Nutrition (Formerly Qualitas Plantarum). 1998. 52(3):231-239.

49. Shalaby M, Mouneir SM. Effect of Zingiber officinale Roots and Cinnamon zeylanicum Bark on Fertility of Male Diabetic Rats. Global Vet. 2010. 5(6):341-347.

50. Lamfon HA. Effect of fenugreek seed extract on carbendazim-inhibited spermatogenesis in albino rats. Journal of Applied Pharmaceutical Science. 2012. 2(04):09-13.

51. Sakr SA, El-Shenawy SM, Al-Shabka AM. Aqueous Fenugreek Seed Extract Ameliorates Adriamycin-Induced Cytotoxicity and Testicular Alterations in Albino Rats. Reproductive Sciences. 2012. 19(1):70-80.

52. Kaviarasan S, Naik GH, Gangabhagirathi R, Anuradha CV, Priyadarsini KI. In vitro studies on antiradical and antioxidant activities of fenugreek (Trigonella foenum graecum) seeds. Food chemistry. 2007. 103(1):31-37.

53. Kassem A, Al-Aghbari A, Al-Habor, M, Al-Mamary M. Evaluation of the potential antifertility effect of fenugreek seeds in male and female rabbits. Contraception. 2006. 73(3):301-306.

54. Collins TFX, Sprando RL, Black TN, Olejnik N, Wiesenfeld PW. Effects of flaxseed and defatted flaxseed meal on reproduction and development in rats. Food and Chemical Toxicology. 2003. 41(6):819-834.

55. Sprando R, Collins TFX, Wiesenfeld P, Babu US, Rees C. Testing the potential of flaxseed to affect spermatogenesis: morphometry. Food and Chemical Toxicology. 2000. 38(10):887-892.

56. Sprando RL, Collins TFX, Black TN, Olejinic N, Rorie JI. The effect of maternal exposure to flaxseed on spermatogenesis in F1 generation rats. Food and Chemical Toxicology. 2000. 38(4):325-334.

57. Hassan AM, Abdel-Wahhab MA. Antioxidant effect of parsley and panax ginseng extract standardized with ginsenosides Rg3 against alteration induced in reproductive functions in male mice. Egyptian Journal of Hospital Medicine. 2006. 22:60-72.

58. Justesen U, Knuthsen P. Composition of flavonoids in fresh herbs and calculation of flavonoid intake by use of herbs in traditional Danish dishes. Food chemistry. 2001. 73(2):245-250.

59. Yang WM, Park SY, Kim HM, Park EH, Park SK. Effects of Panax ginseng on glial cellâe derived neurotrophic factor (GDNF) expression and spermatogenesis in rats. Phytotherapy Research. 2011. 25(2):308-311.

60. Kumar M, Sharma MK, Saxena PS, Kumar A. Radioprotective effect of Panax ginseng on the phosphatases and lipid peroxidation level in testes of Swiss albino mice. Biological and Pharmaceutical Bulletin. 2003. 26(3):308-312.

61. Hwang SY, Kim WJ, Wee JJ, Choi JS, Kim SK. Panax ginseng improves survival and sperm quality in guinea pigs exposed to 2, 3, 7, 8-tetrachlorodibenzop-dioxin. BJU international. 2004. 94(4):663-668.

62. Hwang SY, Kim WJ, Wee JJ, Choi JS, Kim SK .Panax ginseng improves survival and sperm quality inguinea pigs exposed to 2,3,7,8-tetrachlorodibenzop-dioxin. BJU international. 2004. 94(4):663-668.

63. Kang JK, Lee YJ, No KO, Jung EY, Sung JH. Ginseng intestinal metabolite-I (GIM-I) reduces doxorubicin toxicity in the mouse testis. Reproductive Toxicology. 2002. 16(3):291-298.

64. Park JS, Hwang SY, Lee WS, Yu KW, Paek KY. The therapeutic effect of tissue cultured root of wildPanax ginseng CA Mayer on spermatogenetic disorder. Archives of pharmacal research. 2006. 29(9):800-807.

65. Park WS, Shin DY, Kim DR, Yang WM, Chang MS. Korean ginseng induces spermatogenesis in rats through the activation of cAMP-responsive element modulator (CREM). Fertility and sterility. 2007. 88(4):1000-1002.

66. Gonzales GF, Miranda S, Nieto J, Fernández G, Yucra S. Red maca (Lepidium meyenii) reduced prostate size in rats. Reprod Biol Endocrinol. 2005. 3(5):21.

67. Rubio J, Riqueros MI, Gasco M, Yucra S, Miranda S. Lepidium meyenii (Maca) reversed the lead acetate induced--damage on reproductive function in male rats. Food and Chemical Toxicology. 2006. 44(7):1114-1122.

68. Gonzales G, Gasco M, Cordova A, Chung A. Rubio J. Effect of Lepidium meyenii (Maca) on spermatogenesis in male rats acutely exposed to high altitude (4340 m). Journal of endocrinology. 2004. 180(1):87-95.

69. Piacente S, Carbone V, Plaza A, Zampelli A, Pizza C. Investigation of the tuber constituents of maca (Lepidium mey-

enii Walp.). Journal of agricultural and food chemistry. 2002. 50(20):5621-5625.

70. Gonzales GF, Ruiz A, Gonzales C, Villegas L, Cordova A. Effect of Lepidium meyenii (maca) roots on spermatogenesis of male rats. Asian J Androl. 2001. 3(3):231-233.

71. Gonzales G, Córdova A, Vega K, Chung A, Villena C. Effect of Lepidium meyenii (Maca), a root with aphrodisiac and fertility-enhancing properties, on serum reproductive hormone levels in adult healthy men. Journal of endocrinology. 2003. 176(1):163-168.

72. Abd El-Ghany M, Dalia AH, Soha M. Biological study on the effect of pumpkin seeds and zinc on reproductive potential of male rats. Faculty of Specific Education Mansoura University. The 5thArab and 2nd International Annual Scientific Conference. 2010:2384-2403.

73. Abd El-Ghany M, Dalia AH, Soha M. Biological study on the effect of pumpkin seeds and zinc on reproductive potential of male rats. 2010:2384-2403.

74. Banks WA, Coon AB, Robinson SM, Moinuddin A, Shultz JM. Triglycerides induce leptin resistance at the blood-brain barrier. Diabetes. 2004. 53(5):1253-1260.

75. Bjorbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent progress in hormone research. 2004. 59(1):305-331.

76. Gundidza G, Mmbengwa VM, Magwa ML, Ramalivhana NJ, Mukwevho NT. Aphrodisiac properties of some Zimbabwean medicinal plants formulations. African Journal of Biotechnology. 2009. 8(22):6402-6407.

77. Nworgu F, Ekemezie AAO, Ladele AO, Akinrolabu BM. Performance of broiler chickens served heat-treated fluted pumpkin (Telfaria occidentalis) leaves extract supplement. African Journal of Biotechnology. 2007. 6(6):818-825.

78. Aghaie S, Nikzad H, Taghizadeh M, Azami Tameh A, Taherian A. Protective effect of Pumpkin seed extract on sperm characteristics, biochemical parameters and epididymal histology in adult male rats treated with Cyclophosphamide. Andrologia. 2013.

79. Shittu L, Shittu RK, Olufemi O, Tayo AO, Osunubi AAA. Hypoglycaemia and improved testicular parameters in Sesamum radiatum treated normo-glycaemic adult male Sprague Dawley rats. African Journal of Biotechnology. 2009. 8(12):2878-2886.

80. Konan A, Datte J, Yapo P. Nitric oxide pathway-mediated relaxant effect of aqueous sesame leaves extract (Sesamum radiatum Schum. & Thonn.) in the guinea-pig isolated aorta smooth muscle. BMC complementary and alternative medicine, 2008. 8(1):23.

81. Obiajunwa E, Adebiyi F, Omode P. Determination of essential minerals and trace elements in Nigerian sesame seeds, using TXRF technique. Pak. J. Nutr. 2005. 4(6):393-395.

82. Shittu L, Bankole MA, Oguntola JA, Ajala O, Shittu RK. Sesame leaves intake improve and increase epididymal spermatocytes reserve in adult male Sprague Dawley rat. Scientific Research and Essays. 2007. 2(8):319-324.

83. Alonso G, Salinas M, Garijo J. Method to determine the authenticity of aroma of saffron (Crocus sativus L.). Journal of Food Protection. 1998. 61(11):1525-1528.

84. Amini Mahabadi J, Hassani Bafrani H, Nikzad H, Taherian A, Salehi M. Effect of Diet Contains Sesame Seed on Adult Wistar Rat Testis. Int. J. Morphol. 2013. 31(1):197-202.

85. Jeng K, Hou R. Sesamin and Sesamolin: Natures therapeutic lignans. Current Enzyme Inhibition. 2005. 1(1):11-20.

86. Shittu L, Shittu R, Adesite S, Ajala MO, Bankole M. Fitoestregen os Sesame radiatum Estimulan la Actividad Espermatogenica y Mejoran la Calidad del Esperma en el Test ículo de Ratas Sprague Dawley Adulto de Sexo Masculino. International Journal of Morphology. 2008. 26(3):643-652.

87. Khaki A, Fathiazad F, Nour, M, Khamenehi H, Hamadeh M. Evaluation of androgenic activity of allium cepa on spermatogenesis in the rat. Folia morphologica. 2008. 68(1):45-44.

88. Nemeth K Piskula M. Food content, processing, absorption and metabolism of onion flavonoids. Critical reviews in food science and nutrition. 2007. 47(4):397-409.

89. Izawa H, Kohara M, Aizawa K, Suganuma H, Inakuma T. Alleviative effects of quercetin and onion on male reproductive toxicity induced by diesel exhaust particles. Bioscience, biotechnology, and biochemistry,. 2008(0):804020843.

90. Chakrabarti K, Pal S, Bhattacharyya AK. Sperm immobilization activity of Allium sativum L. and other plant extracts. Asian journal of andrology. 2003. 5(2):131-136.

91. Sultana S, Ahmed S, Jahangir T, Sharma S. Inhibitory effect of celery seeds extract on chemically induced hepatocarcinogenesis: modulation of cell proliferation, metabolism and altered hepatic foci development. Cancer letters, 2005. 221(1):11-20.

92. Hamza AA, Amin A. Apium graveolens modulates sodium valproateâ€‐induced reproductive toxicity in rats. Journal of Experimental Zoology Part A: Ecological Genetics and Physiology. 2007. 307(4):199-206.

93. Charles DJ, Simon JE, Wood KV, Heinstein P. Germplasm Variation in Artemisinin Content of Artemism annua Using an Alternative Method of Artemisinin Analysis from Crude Plant Extracts. Journal of natural products. 1990. 53(1):157-160.

94. Ajah P Eteng M. Phytochemical screening and histopathological effects of single acute dose administration of Artemisia annua L. on testes and ovaries of Wistar rats. African Journal of Biochemistry Research. 2010. 4(7):179-185.

95. Phillips OA, Mathew KT, Oriowo MA. Antihypertensive and vasodilator effects of methanolic and aqueous extracts of Tribulus terrestris in rats. Journal of ethnopharmacology. 2006. 104(3):351-355.

96. Karimi Jashni H, Malekzadeh Shiravani S, Hoshmand F. The effect of the Tribulus terrestris extract on spermatogenesis in the rat. Journal of Jahrom University of Medical Sciences. 2012. 9(4):9.

97. Gauthaman K, Ganesan AP. The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction - an evaluation using primates, rabbit and rat. . Phytomedicine. 2008. 15(1):44-54.

98. Gauthaman K, Ganesan AP, Prasad R. Sexual effects of puncturevine (Tribulus terrestris) extract (protodioscin): an evaluation using a rat model. The Journal of Alternative & Complementary Medicine. 2003. 9(2):257-265.

99. El-Tantawy WH, Temraz A, El-Gindi OD. Free serum testosterone level in male rats treated with tribulus alatus extracts. International braz j urol. 2007. 33(4):554-559.

100. Park SW, Lee CH, Shin DH, Bang NS, Lee SM. Effect of SA1, a herbal formulation, on sexual behavior and penile erection. Biological and Pharmaceutical Bulletin. 2006. 29(7):1383-1386.

101. Jashni HK, Shiravani SM, Hooshmand F. The effect of the Tribulus terrestris extract on spermatogenesis in the rat. Journal of Jahrom University of Medical Sciences. 2012. 9:7-11

102. Esfandiari A, Dehghani R. Histomorphometrical study of seminiferous tubule in rats after used Tribulus terresteris. Journal of Cell and Animal Biology. 2010. 4(2):068-072.

103. Golalipour MJ, Kabiri Balajadeh B, Ghafari S, Azarhosh R. Protective effect of urtica dioica L.(urticaceae) on morphometric and morphologic alterations of semiferous tubules in stz diabetic rats. Iranan Journalof Basic Medical Sciences.2011. 14(5): 472–477

104. Mavi A, Terzi Z, Ezgen U, Yildirim A. Antioxidant properties of some medicinal plants: Prangos ferulacea (Apiaceae), Sedum sempervivoides (Crassulaceae), Malva neglecta (Malvaceae), Cruciata taurica (Rubiaceae), Rosa pimpinellifolia (Rosaceae), Galium verum subsp. verum (Rubiaceae). Urtica dioica (Urticaceae). Biological and Pharmaceutical Bulletin, 2004. 27(5):702-705.

105. Ghafari S, Balajadeh BK, Golalipour M. Effect of Urtica dioica L.(Urticaceae) on Testicular Tissue in STZ-induced Diabetic Rats. Pakistan Journal of Biological Sciences. 2011. 14:798-804.

106. Swamy S, Tan B. Cytotoxic and immunopotentiating effects of ethanolic extract of Nigella sativa L. seeds. Journal of ethnopharmacology. 2000. 70(1):1-7.

107. El-Mahmoudy A, Matsuyama H, Borgan MA, Shimizu Y, El-Sayed MG. Thymoquinone suppresses expression of inducible nitric oxide synthase in rat macrophages. International immunopharmacology, 2002. 2(11):1603-1611.

108. Mohammad MA, Mohamad MMJ, Dradka H. Effects of Black Seeds (Nigella Sativa) on Spermatogenesis and Fertility of Male Albino Rats. Research Journal of Medicine and Medical Sciences. 2009. 4(2):386-390.

109. Ghosheh OA, Houdi AA, Crooks PA. High performance liquid chromatographic analysis of the pharmacologically active quinones and related compounds in the oil of the black seed (Nigella sativa L.). Journal of pharmaceutical and biomedical analysis. 1999. 19(5):757-762.

110. Cheikh-Rouhou S, Besbes S, Hentati B, Blecker C, Deroanne C. Nigella sativa L Chemical composition and physiochemical characteristics of lipid fraction. Food chemistry. 2007. 101(2):673-681.

111. Bashandy AES. Effect of fixed oil of Nigella sativa on male fertility in normal and hyperlipidemic rats. International Journal of Pharmacology, 2007. 3(1):27-33.

112. Wendel AA, Belury MA. Effects of conjugated linoleic acid and troglitazone on lipid accumulation and composition in lean and Zucker diabetic fatty (fa/fa) rats. Lipids. 2006. 41(3):241-247.

113. Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, Crocus sativus stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats. Phytomedicine. 2008. 15(6-7):491-495.

114. Modaresi M, Mesripour M, Asadi Margh Maleki M, Hamedanian MK. Effect of Saffron (Crocus Sativus) extract on level of FSH, LH and testosterone in mice. Journal of Zanjan University of Medical Sciences and Health Services. 2008. 16(63):11-17.

115. Modaresi M , Mesripour M, Asadi Margh Maleki M, Hamedanian MK. The effect of saffron extract on testis tissue. Iranian Jornal of Medicinal and Aromatic Plants. 2008. 24:237-243.

116. Assimopoulou A, Sinakos Z, Papageorgiou V. Radical scavenging activity of Crocus sativus L. extract and its bioactive constituents. Phytotherapy Research. 2005. 19(11):997-1000.

117. Abdullaev F, Riveron-Negrete L, Caballero-Ortega H, Manuel Hernandez J, Perez-Lopez I. Use of in vitro assays to assess the potential antigenotoxic and cytotoxic effects of saffron (Crocus sativus L.). Toxicology in vitro. 2003. 17(5-6):731-736.

118. Shamsa A, Hosseinzadeh H, Molaei M, Shakeri MT, Rajabi O. Evaluation of Crocus sativus L.(saffron) on male erectile dysfunction: A pilot study. Phytomedicine. 2009. 16(8):690-693.

119. Kaya S, Tekin AR. The effect of salep content on the rheological characteristics of a typical ice-cream mix. Journal of Food Engineering. 2001. 47(1):59-62.

120. Thakur M, Thompson D, Connellan P, Deseo MA, Morris C. Improvement of penile erection, sperm count and seminal fructose levels in vivo and nitric oxide release in vitro by ayurvedic herbs. Andrologia. 2011.

121. Esteves SC, Miyaoka R, Agarwal A. An update on the clinical assessment of the infertile male. Clinics (Sao Paulo). 2011. 66:691-700.