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A Review on Medicinal Plants Used for Improvement of Spermatogenesis

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Abstract

Male factor infertility accounts for 40% of infertility cases. Spermatogenetic failure, including azoospermia and oligospermia, is one of the important causes of male infertility. Among different methods, medicinal plants have been used in many Nations to treat male infertility problems. So in this review, we have summarized most of the data dealing with the positive effects of plant extracts on spermatogenesis.

Keywords: Spermatogenesis; Infertility; Medicinal plants

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]. Male infertility is affected by a variety of environmental, behavioral, genotoxic and genetic factors, resulting in an impaired spermatogenesis at various stages [4]. Testicular spermatogenesis comprises a precisely timed and synchronized development of several generations of germ cells involving spermatogonial mitosis (proliferative phase); spermatocyte in which genetic material is recombined and segregated (meiotic phase); morphological transformation of the undifferentiated spermatids into highly specialized motile sperms (spermiogenic phase) [5]. Factors that impaired can be divided into several categories that include: 1. Foetal determinants of spermatogenesis in adulthood (e.g. reduced sertoli cell proliferation and final number, reduced perinatal germ cell development, Testicular germ cell cancer and testicular dysgenesis syndrome), 2. Lifestyle effects on spermatogenesis in adulthood; among them scrotal heating, obesity, smoking, alcohol and drugs and 3. Exposure to environmental chemicals in adulthood such as occupational exposures, pollutants is well defined causes of impaired spermatogenesis and male infertility [6].

Various chemical drugs are available to treat infertility; however, researchers are looking for drugs with less adverse effects and toxicity. In developing countries, traditional medicine is important in maintaining health of population [7]. The aim of this article is to critically review the available literature on herbal medicines and their possible roles in improvement of spermatogenesis.

Spermatogenesis

In mammalian testis Spermatogenesis takes place in the seminiferous tubules which are composed of Sertoli cells (SCs) and maturing germ cells surrounded by one (rodents) or more (large animals) layer(s) of peritubular myoid cells [8,9]. Spermatogenesis is a complex and highly organized process where germ cells undergo three phases of development: mitosis (spermatogonial proliferation), meiosis (spermatocyte DNA recombination, reduction and division), and spermiogenesis (spermatid differentiation); resulting in the transformation of the undifferentiated spermatogonia into highly specialized spermatozoa [10]. In rodents, the spermatogonial population is divided into two main categories. (1) Undifferentiated consisting of type A_{single}, A_{paired} and $A_{aligned}$ and (2) differentiated consisting of A1–A4, Intermediate and type B [10,11]. In primates and humans, the spermatogonial hierarchy consists of two main populations of type A undifferentiated spermatogonia: A_{dark} and A_{pale}. The A_{pale} spermatogonia undergo mitotic divisions to produce type B1 spermatogonia [10,11]. In all mammals, the type B/B1 spermatogonia undergo mitosis to give rise to the cells that represent the beginning of meiosis, the preleptotene spermatocytes. The preleptotene spermatocytes enter prophase I of meiosis, transform into leptotene, zygotene, pachytene and diplotene cells, which then quickly finish meiosis I forming secondary spermatocytes. While advancing through the long meiotic prophase I, spermatocytes undergo several changes such as chromosome condensation, genetic recombination and migration from the basal to the adluminal compartment of the seminiferous tubule through the BTB/SC barrier [10]. The second meiotic division, meiosis II, rapidly follows meiosis I to produce haploid cells, the spermatids [10,11]. Spermatids differentiate into spermatozoa by proceeding through spermiogenesis, before being released into the lumen [10]. These processes are accompanied by the migration developing spermatids from the basal compartment towards the edge of the tubule lumen so that fully developed spermatids (i.e., spermatozoa) can be emptied into the lumen at spermiation [12].

Medicinal plants and Spermatogenesis

A medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs [13]. Medicinal plants are used for the treatment of various diseases in several decades. They were shown to be good, effective, inexpensive, safe, and available. Currently, extraction and development of several drugs and chemotherapeutics from these plants have been widely observed [14]. Plant sourced food antioxidants like vitamin C, vitamin E, carotenes,

phenolic acids, phytate and phytoestrogens have been recognized as having the potential to reduce disease risk that can scavenge free radical. Researchers suggest that two-thirds of the world's plant species have medicinal value and many of them have great antioxidant potential many plant species have similar antioxidant potentials as that of synthetic antioxidant without potential. Side effect and are used as an alternative in the food processing industry and in preventive medicine [15]. We studied the effects of different plants which have positive effects on spermatogenesis.

Alpinia galanga

The plant species *Alpinia galanga* belongs to the family of Zingiberaceae is a perennial herb with rhizomatous root stocks and is mainly known in Asia (China, India, Indonesia, Japan, Malaysia and Thailand), as a drug prepared from the rhizomes and roots and is used as tea or tincture with spasmolytic, antiphlogistic and antibacterial effects, also is used as stomachicum and against gastric diseases [16]. This species, like other spices is rich in phenolic compounds such as flavonoids and phenolic acids and also rich in alcoholic extract such as cineole, methyl cinnamate, myrecene and contains various flavones such as galangin, alpinin, kampferide and 3-dioxy-4-methoxy [17].

The phyto-pharmacological activity of *A. Galanga* as antioxidant and anticancer property has well been reviewed [18,19]. Antioxidants protect DNA and important molecules from oxidative damage and can improve sperm quality and consequently enhance fertility rate in men [20] in a study, it was shown that A. galangal rhizome treatment for the (300 mg/kg) 56 days affected sperm parameters and spermatogenesis process in rats; however this extract did non causes an increase in testes weight of rats. The extract had a direct effect on the testes resulting in an increase in the number of spermatozoa and the increased level of testosterone production [21].

Apium graveolens

Apium graveolens (Celery) belongs to the parsley (Umbelliferae) species from the Apiaceae family, with a height of 100 cm, and a strong scent and fleshy and solid stems [22].

Based on available reports, plants such as celery contain phytoestrogens, which can be effective in fertility and reproductive system [23]. Furthermore, a study indicated that celery has a protective effect on testes against sodium valproate [24] and di (2-ethylhexyl) phthalate [25]. Studies demonstrated that celery protects testes from functional and structural damages and sperm from toxicity induced by atrazine [26] and quinine sulfate [27]. In a study, administration of 200 and 300 mg/kg to rats for 60 days showed a significant increase in the number of sperms, sertoli cells, and primary spermatocyte compared to the control group. It seems that celery increases spermatogenesis in male rats, but has no destructive effects on testicular tissue [28].

Phoenix dactylifera. L.

Date Palm Pollen (DPP) has been used for many years in folk medicine in Middle East and some Asian countries for promotion of good health and improving male or female fertility [29-31]. In a study, administration of 120 mg/kg and 240 mg/kg DPP to rats for 35 days showed a significant increase in sperm count, sperm motility and estradiol level compared to the control group. Also, STD increased in 120, 240 and 360 mg/kg [32]. Phytochemical studies have been confirmed presence of estrone, α-amirin, triterpenoidal saponins and flavonoids in DPP [33-35]. DPP extracts also contain cholesterol, rutin, carotenoids, oestrones- gonad stimulating components that can improve male infertility and elicit gonadotrophin activity [33,36]. Alkaloids of DPP also have estrogenic properties [37]. It is also known that the estradiol components of DPP play an effective role in regulating the renewal of spermatogenic cells and male reproductive tissues that possess estrogen receptors [33].

Danae racemose

In a study, administration of 200 mg/kg and 400 mg/kg *Danae racemose* to rats for 28 consecutive days, significantly increased the sperm motility and viability in both experimental groups compared with the control group. Caudal epididymal sperm count was significantly increased after 28 days treatment in a dose (400 mg/kg) and duration-dependent manner compared with the control group. *Danae racemosa* extract daily for 28 consecutive days significantly decreased level of Malondialdehyde (MDA) concentration in experimental groups compared to control group. Therefore suggested increased use of *Danae racemosa* extract can decrease side effects of sperm abnormality and increased sperm parameters in male infertile man's [38].

Citrullus vulgaris

Citrullus vulgaris (Watermelon Seed Extract) Watermelon has numerous antioxidants (e.g. lycopene, beta carotene) and some specific amino acids (e.g. arginine, citrulline) [39]. Several studies have reported that antioxidants and vitamin A, B, C, and E in diet can protect sperm DNA from free radicals and increase blood-testis barrier stability [40,41]. Administration of 55 mg/kg *Citrullus vulgaris* extract for 28 consecutive days significantly increased Sperm concentrations, motility and viability in experimental group as compared with the control group [42].

Cinnamomum zeylanicumon

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 and cytotoxic 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 [43]. Khaki demonstrated that the Administration of 75 mg/kg *C. zeylanicum* for 28 days significantly increased sperm concentration, motility and viability in the experimental group compared to controls. Serum total testosterone was also increased after exposure to *C. zeylanicumon* extract [44]. 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 [45].

Aloe vera

Aloe is a cactus like perennial herbaceous plant which grows easily in arid warm regions of Africa, North America, Europe and Asia. *Aloe vera* is a pharmaceutical plant which can be useful for curing various diseases and improving body's physiology [46]. *Aloe vera* can enforce its antioxidant role indirectly via strengthening vitamin C and E [47].

This plant has also many uses in traditional medicine including: orally, as a laxative to treat constipation (in patients with anal fissures, hemorrhoids and anorectal surgery) and also for preputation of diagnostic tests for gastrointestinal disease curing gastric ulcer, tuberculosis, fungal infection and decreasing blood glucose, minor skin irritation, including burns and second degree burns from thermal radiation, bruises and scratches. Administration of 100 mg/kg and 200 mg/kg to rats for 20 days significantly increased the number of stem cells and primary spermatocytes compared to control group [48]. One important factor which has probably affected and increased stem cells and primary spermatocytes is anti-apoptosis factor in *Aloe vera* extract can affect spermatogenesis directly via affecting germinal cells and stimulating cell division. It can also affect indirectly via stimulating leydig cells and increase in testosterone hormone [47]. flavonoids are from phytoestrogens which are natural herbal compounds with an estrogen-like structure vitamin E prohibits reduction in number of leydig and sertoli cells and increases in testosterone. Also this vitamin improves testis weight, seminiferous tubule diameter and thickness of the germinal epithelium [49].

Phaleria macrocarpa

Phaleria macrocarpa (Mahkota Dewa) is one of the herbs that have been used in traditional herbal medicine that was originally found in Papua, Indonesia. It is commonly used for the treatment of various ailments such as cancer, diabetes, hypercholesterolemia, hypertension, heart disease, allergy and etc. [50]. It's fruits contain natural chemical compounds like alkaloid, saponin, flavoid, and polyphenol and each of the compounds has its own function [51]. In a study, administration of 240 mg/kg of *P. macrocarpa* aqueous extract for seven weeks in male adult rats lead to the improvement of rat's infertility as evidenced by significantly increased spermatogonia cells number and thickness of seminiferous tubules compared to control group [52]. According to Djannah, *P. macrocarpa* fruit contains alkaloid, flavonoid and saponin which can influence the microanatomic structure of the testis of male mouse [53]. Gauthaman et al. has shown that saponin component of plants enhances aphrodisiac properties because they have stimulatory effect on androgen production [54].

Ocimum basilicum

Basil (*O. basilicum* L., family Lamiaceae) is used as a kitchen herb and an ornamental plant in the house garden [55]. *Ocimum basilicum* (Basil) is an annual herb of the Lamiaceae family, which is widely cultivated in Asia as a nourishing food and herbal medicine. *O. basilicum* is widely used in folk medicine to treat a wide range of diseases. For example, the aerial part of *O. basilicum* is traditionally used as an antispasmodic, aromatic, digestive, carminative, stomachic and tonic agent [56]. Administration of 1.5 and 3 g/kg body weight *O. basilicum* extract for 40 consecutive days significantly increased sperm motility, viability and count only in the extract treated group, when compared with the control. It has been demonstrated that *O. basilicum* extract significantly decreased the concentration of the malondialdehyde (MDA) level in the treatment groups when compared with the control group. Total antioxidant capacity (TAC) was significantly increased in the extract groups, when compared with group. These results confirmed previous chemical studies of herbal antioxidant effects [57] from *O. basilicum* ingestion, due to the presence of flavonoids, phenylpropanoids, and rosmarinic acid in the aerial parts of the plant [58,59]. These reports also documented the antioxidant and radical scavenging activity of *O. basilicum* [60,61].

Zingiber Officinale

Zingiber Officinale (Ginger) is common is name for plant belongs to family Zingiberaceae, which contains about 1300 species in 50 genera, along with four other families is placed in the order Zingiberales [62]. Ginger is a plant that comes from south-east Asia, and also in cultivated in Africa, China, India and Jamaica [63,64]. Chemical constituents of ginger classified to volatile oils (including borneol, camphene, citral, eucalyptol, linalool, phenllandrene, zingiberine and zingiberolpenols (gingerol, zingerone and shogaol) and resin) which constitutes (1-3%) mainly of zingeberene nonvolatile pungent compounds oleo-resin constitutes (4-7.5%) mainly gigerols and other constituents with more than 50% of starch [63,65]. Ginger extract has recently been shown to have a variety of biological activities, including anticancer, anti-oxidation, anti-inflammation and antimicrobial properties [66-68]. Ginger extracts have also been reported to have a potent androgenic activity in male rats. Human hormone that plays an important physiological role in the regulatory and tissue rebuilding mechanisms related to estrogen effects, as well as acting as an intermediate in the biosynthesis of androgens, estrogens, and corticoids. It is also used as the precursor of vitamin D3 [69]. In a study Administration of 50 mg/kg/mouse and 100 mg/kg/mouse ginger for 22 consecutive days significantly increased Sperm motility and viability in both experimental groups as compared with the control group. The lumen in experimental groups the seminiferous tubules showed a significant increase in the luminal spermatozoa [70]. In the other study [71,72], administration of 50 mg/kg or 100 mg/kg/rat ginger for 20 days significantly increased sperm functions (sperm count, motility, viability) and concentrations in rat. Ginger has protective effects against oxidative stress in rat.

Punica granatum

Punica granatum (Pomegranate) has been used in the folk medicine of many cultures especially in the Middle East [73]. Edible parts of pomegranate fruit represent 52% of total fruit weight, comprising 78% juice and 22% seeds. Fresh juice is rich in vitamin C and polyphenolic compoundssuch as anthocyanins, punicalagin, ellagic and gallic acid [74,75]. Pomegranate has become more popular because of the attribution of important physiological properties, such as anticancer [75,77] antiproliferative, apoptotic [74] HIV-I entry inhibitory, topical microbicidal [78] cardioprotective [79] antihyperlipidemic [80] and etc. Additionally, many investigators [81,82] have reported that pomegranate and its derivatives have free radical scavenger and potent antioxidant activity. Administration of 0.25 mL PJ plus 0.75 mL distilled water (PJ-low), 0.50 mL PJ plus 0.50 mL distilled water (PJ-middle) and 1 mL PJ (PJ-high) to rats for seven weeks showed significantly increased the diameter of ST and germinal cell layer thickness when compared to the control group [83]. The presence of degenerating spermatogenic cells that can be present in normal testis was less in rats that received different doses of PJ, especially middle and high doses when compared to the control. However; Sertoli and Leydig cell concentrations were not affected by PJ administration. Spermatogenic cell density and sperm quality increased because increased antioxidant capacity protected spermatozoa against peroxidative damage in healthy rats. Hence, it can be said that there is a positive relation between PJ consumption and sperm parameters [83].

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 [84]. *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 [85,86]. *N. sativa* seeds have much unsaturated (linoleic and oleic acid) and essential fatty acids [87]. The seeds contain carotene calcium, iron, and potassium [86]. *Nigella sativa* has hypoglycemic effect [88], and used as immunopotentiating, immunomodulating and interferon like activities [89,90], as well as it' s action in amelioration of reproductive performance of rats [91] and female mice [92] and its role in correcting the CNS functions by the abilities of Thymoquinone TQ to minimize the tension of epilepsy in rats when black seed used as an anticonvulsant, muscle relaxant, analgesic and CNS depressant activity [93-95]. Most of the pharmacological activities are attributed to the presence of thymoquinone as an active component [96]. Thymoquinone possess antioxidant effects through enhancing the oxidant scavenger system as well as its potent anti-inflammatory mediators, prostaglandins and leukotrienes [97]. In a study treatment with alcoholic extract of *Nigella sativa* (0.5 and 1.5 g/kg) led to significant increase in body weight gain (g), reproductive parameters (seminiferous tubules thickness and diameters, account of spermatogonia, primary and secondary spermatocytes, spermatids, free spermatozoa, account of sertoli and Leydig cells, diameter of Leydig cells and the height of epithelial cells entirely covered epididymal caudal), hormones (testosterone and follicle stimulating hormone) as well as protein concentration [98]. The results of this study was in agree with [99] who reported that black seed contain alkaloids and phenols which stimulate the secretion of FSH and Testosterone. The increase in sperm concentration was due in part to the increase in testosterone and FSH levels in testicular tissue; since these two hormones were responsible for spermatocytogenesis and spermiogenesis in seminiferous tubules, while testosterone is responsible for epididymal function in maturation of sperms [100].

Cardiospermum halicacabum

Cardiospermum halicacabum (Welpenela in Sinhala; balloon vine in English) is an annual or sometimes perennial herb, which is very common in the low country of SriLanka. The roots are used for nervous diseases [101] and as a diaphoretic, diuretic, emetic, emmenagogue, laxative, refrigerant, stomachic, and sudorific [102]. Fresh leaf juice is given for asthma patients and it can also reduce obesity. The leaves also are used as one of the ingredients in a medicine for abnormal suppression of menstrual cycle. Leaves boiled in oil such as castor oil are applied over rheumatic pain swellings and tumors of various kinds [103]. Phytochemical constituents such as flavones, aglycones, triterpenoids, glycosides, and a range of fatty acids and volatile ester have been reported from the various extracts of this plant [104]. In a study, administration of Aqueous Leaf Extract of *Cardiospermum halicacabum* (L.). Total sperm count in cauda epididymis and percentage of motile sperm showed significant increase in treatment group A (200 mg/kg) and group B (100 mg/kg) when compared to the control. However treatment with 2 doses of ALE did not significantly change the organ weights of epididymes, testes, and seminal vesicles compared to the control [105].

Withania somnifera

Ashwagandha (*Withania somnifera*), also known as "Indian ginseng" due to its rejuvenating effects, has been described in folk medicine as an aphrodisiac and geriatric tonic [106]. Ashwagandha is rich in a wide variety of chemical compounds, such as alkaloids, ergostane steroids, amino acids, and neurotransmitters, which explains it's numerous medicinal properties that can directly or indirectly prevent and treat a number of diseases [107-109]. Different investigators have reported that Ashwagandha is beneficial in the treatment of male infertility [110,111]. In a study, treatment with a high-concentration, full-spectrum root extract of Ashwagandha (225 mg/kg) for 90 days resulted in significantly improved semen parameters in concert with improved and regulated sexual hormone levels in oligospermic males [112].

Discussion

Spermatogenetic failure, including azoospermia and oligospermia, is one of the important causes of male infertility [113]. Several conditions can interfere with spermatogenesis and reduce sperm quality and production. Many factors such as drug treatment, chemotherapy, toxins, air pollution and vitamins insufficient intake may have harmful effects on spermatogenesis and sperm normal production [114-117]. Researches have reported that using antioxidants and vitamins A, B, C, and E in daily diet can protect sperm DNA from free radicals and increase blood testis barrier stability [118]. Several studies have reported that antioxidants and vitamin A, B, C and E in diet can protect sperm DNA from free radicals and increase blood testis barrier stability [119]. 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 and viability); increasing Leydig cell counts, seminiferous tubule diameters, decreasing abnormal sperm and improving histopathological recovery and sexual stimulation (erection, intromission and ejaculatory latency); increasing concentration and motility of sperm in ejaculation volume [120].

Conclusion

Various herbs have been used by people of different cultures to treat conditions of male infertility or for treatment of reproductive disorders. Investigations in validation of the herbs will go a long way in management of infertility. Moreover; the cross talk of various pathways involved must also be taken into account to come up with a molecular pathway to find a lead molecule of herbal origin of the treatment of various forms of sexual dysfunction. Also further studies should be done on the cellular level and intracellular signaling pathways to understand the mechanism of plant extracts to be improvement of spermatogenesis.

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