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Sexual Abnormalities in Males and Their Herbal Therapeutic Aspects

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ABSTRACT

The inability to have child is a personal tragedy and a large proportion of childless people are confronted with social stigmatization and frustration. Erectile dysfunction is one of the commonest disorders of male sexual function. Among the methods used to treat male infertility problems, medicinal plants have been used empirically as extracts, decoctions, fractions or semi-purified compounds. These herbal products are used in the treatment of a dysfunctioning of the libido, sexual asthenia, erection and sperm disorders. Penile erection depends on a complex interaction of psychological, neural, vascular and endocrine factors. Testosterone has an important role in both central and peripheral domains of this process. Pharmacological activities of many plants have been shown *in vitro* using cells, *in vivo* (on laboratory animals) and human studies. Plants provide a treatment option that is affordable and available for infertile couples and phytotherapy is an essential form of treatment in our health system .In this review, we have summarized most of the data dealing with role of testosterone and the effects of plant extracts on mammalian reproductive functions.

Key words: Sexual dysfunction, herbal, review, reproductive, infirtile couples

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INTRODUCTION

Around the world one out of six couples trying to conceive has difficulties. Formerly assigned to women, infertility of a couple is equally distributed between two sexes. On evaluation roughly 50% of the affected couples have causal or associated male factors as a cause of infertility[1]. Male sexual disorder is common worldwide among men of all ages, ethnicities and cultural backgrounds. Although, MSD rarely threatens physical health, it can take a heavy physiological toll, bringing on depression, anxiety and debilitating feelings of inadequacy. Sexual dysfunction in men takes different forms such as disorders of desire (persistently or recurrently deficient sexual fantasy and desire for sexual activity), disorders of orgasm (persistent or recurrent delays in or absence of orgasm after a normal sexual excitement phase), erectile dysfunction (persistent failure to generate sufficient penile body pressure to achieve vaginal penetration and the inability to maintain this degree of penile rigidity until ejaculation), disorder of ejaculation (persistent or recurrent ejaculation with minimum sexual stimulation that occurs before, upon or shortly after penetration and before a person wish it or a situation where ejaculation does not occur at all) and failure of detumescence (Prolonged priaprism lasting for more than 4 h). MSD is of varied etiologies and these includes personal life style (chronic alcohol abuse, cigarette smoking), androgen deficiency, aging, psychological disorders, side effects of some antihypertensive drugs, central agents, psychiatric medications, antiulcer antidepressants and antiandrogens and chronic medical conditions like diabetes, hypertension and pulmonary cancer[2].

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Physiology of erection: Erection is a complex, involuntary, neuropsychological, hormone-mediated vascular event. Normal sexual function in men can be conceptualized into four serial domains: sexual desire/interest (collectively called libido for the purpose of this article), erection, ejaculation/orgasm and detumescence. The physiological functional integrity of the sexual organ is dependent not only on its nervous (autonomic and somatic innervations of the penis) and muscular tissues of the corpora cavernosa but also on the endocrine and psychic factors from higher centre of the brain. A spontaneous sexual act represents the final manifestations of a series of complex and meticulously synchronized processes.

An erection occurs in response to external erotic stimuli relayed via any of the five senses or self-generated fantasy, which result in inhibition of sympathetic and activation of parasympathetic tone of the pelvic autonomic nerves and release of Nitric Oxide (NO) from Non-adrenergic Noncholinergic (NANC) nerve endings in the cavernosal endothelial cells. NO activates

guanyl cyclase thereby generating cyclic guanosine monophosphate (cGMP). cGMP decrease calcium uptake into vascular and cavernosal smooth muscle inducing relaxation, which in turn causes blood filling of the spaces of corpora cavernosa and penile engorgement. This expansion of the sinusoids exerts pressure on the veins that normally drain blood from the penis. The pressure is adequate to close the veins thus trapping the blood in the penis. The result is increase in circumference, rigidity and elongation of the penis. Phosphodiesterase-5 enzyme converts cGMP to inactive GMP initiating detumescence.

ENDOCRINE CAUSES OF ERECTILE DYSFUNCTION

Many endocrine disorders can cause ED directly and indirectly including diabetes, hypogonadism, thyroid dysfunction, adrenal diseases, hyperprolactinaemia, obesity and iatrogenic causes. The hypothalamo-pitutary-testis axis is the most important endocrine system affecting male sexual function. The attribution of hypogonadism has been estimated from 2.1-21%. This discrepancy derives from differences in definition of ED, demographic characteristics of patients, diagnostic and inclusion criteria in different studies. As most endocrinologic causes of ED are treatable, every effort should be made to exclude potential hormonal aetiologies underlying ED at an early stage.

ERECTILE DYSFUNCTION

Erectile Dysfunction (ED) is one of the commonest disorders of male sexual function and an underline cause for infertility. For there to be normal sexual intercourse in males, the sexual organs and factors relating to erection of the copulatory organ must function normally. ED is defined as persistent or recurrent inability to attain penile erection sufficient for satisfactory sexual performance. It is estimated that more than 152 millions men worldwide experienced ED in 1995 and that this number will rise by 170 millions to approximately 322 millions by the year 2025[3].

PLANTS IN TREATMENT OF MSD

Testosterone and libido

Testosterone and libido-human studies: A number of studies, using young hypogonadal men as an experimental model, confirmed the positive effect of testosterone on the central domain of male sexual function. In these patients, withdrawal and reintroduction of exogenous androgens affected the frequency of sexual fantasies, sexual arousal and desire, Nocturnal Penile Tumescence (NPT), sexual activities and orgasm[4,5,6,7,8,9,10]. Seventeen randomized placebo-controlled trials have been systematically reviewed in an excellent meta-analysis giving details of 656 patients: 248 treated with testosterone and 372 treated with placebo for a median of 12 weeks (4 weeks to 36 months). In hypogonadal subjects, testosterone consistently improved the number of morning erections, sexual thoughts, motivation and sexual satisfaction, number of successful intercourses, spontaneous erectile function and the overall sexual satisfaction with an overall strong effect size [standard mean difference 0.92 (0.71-1.13)[11]. Because this interval is far from zero, there is an indication that testosterone treatment in hypogonodal men is effective.

There is only limited evidence on the effect of testosterone administered to eugonadal men with or without sexual problems. The effects of testosterone treatment, including supraphysiological doses used as male hormonal contraception in eugonadal young men was limited to minor increases in sexual thoughts and desire[12,13].

Collectively, the evidence from hypogonadal patients[4,6,11], eugondal men rendered hypogonadal[14] and transsexual patients undergoing cross-gender reassignment[15]. Sex hormone therapy consistently testifies to the key role of testosterone in the establishment and maintenance of the central domain of male sexual function and also secondarily erection in response to psychosexual stimulation.

PLANTS AND LIBIDO IN RODENTS AND HUMANS

The ethanolic extract of *Vanada tessellate* flowers at a dose of 50 and 200 mg kg^{-1} increased the mating performances in male mice[16]. The extract of *Tribulus terrestris* (5mg kg^{-1} for eight weeks of treatment) stimulated rat libido (sexual desire)[17]. Roots of *Panax Ginseng* or *Panax quinquefolius* at a dose of 100 mg kg^{-1} for 28 days increased physical strength and vitality-decreased in mount, intromission and ejaculation latencies and the plasma prolactin levels in normal male rats[18]. Extract of *Eurycoma longifolia* given to castrated male rats at a dose of 200, 400 and 800 mg kg^{-1} twice daily for 10 days stimulated sexual arousal[19]. Seed extracts of *Terminala catappa* increased sexual vigor which included mounting frequency and intromission frequency along with sexual performance (intercopulatory intervals) of rats at the dose of 1.5 mg kg^{-1} after seven days of treatment[20].

The extracts of *Turnera diffusa* and *Paffia paniculata* administered to sexually sluggish or impotent rats at the dose of 1 mL kg^{-1} per 2 h before testing, stimulated mating and ejaculatory performances reduced mounting, intromission and ejaculatory latencies[15]. The ethanolic extract of *Trichopus zeylanicus* at the dose of 200 mg kg^{-1} increased mating performances in male mice 1, 2 and 3 h and 6 days after administration[21]. The bark extract of

Butea frondonsa given at the dose of 400 mg kg^{-1} to male reduced mount, intromission, ejaculation latencies and post ejaculatory intervals after 21 and 28 days of treatment. It also increased the mounting, intromission and ejaculatory frequencies[22]. The alcoholic extract of *Myristica fragrans* seeds at a dose of 500 mg kg^{-1} given for 7 days. The extract of *Epimedium koreanum* at a dose of 300 and 750 mg kg^{-1} for a 10 day treatment increased mating and intromission frequencies, decreased the intromission and post-ejaculation[24]. The aqueous root extract of *Dactylorhiza hatagirea* at a dose of 200 mg kg^{-1} after 28 days of treatment stimulated rat libido, mating and ejaculatory frequencies, increased testosterone level and decreased the intromission and postejaculatory latencies[25]. Moreover aqueous extract of *Montanoa tomentosa* at a dose level of 75 mg kg^{-1} stimulated sexual arousal and increased mounting behavior in genitally anaesthetized animals, 30 min after administration. *Ginkgo biloba* at a dose of 50 mg kg^{-1} given to male rats for a period of 14 or 28 days increased ejaculatory frequency and reduced ejaculatory latency but a significant reduction in serum prolactin levels was also observed[26]. *Casimiroa edulis* at a dose of 250 mg kg^{-1} redced mounting post-ejaculatory intervals and intromission latency and increased mounting and intromission frequencies[27]. The extract of *Catha edulis* at dose of 100 mg kg^{-1} reduced mounting and intromission latency thereby enhancing sexual motivation/arousal in male rats after 15 days of treatment[28].

The ethanolic extract of Dracaena arborea at a dose of 100 mg kg^{-1} for 7 and 14 days increased erection, mounting and intromission frequencies in normal and castrated rats[29]. Epimedium brevicornum Maxim at a concentration of 30, 300 and 1000 microgram mL^{-1} for 20 min of incubation has been shown *in vitro* to relax the corpus carvenosum smooth muscle precontracted with phenylephrine in a concentration dependent manner, increased the amount of cGMP product and potentiated the phosphodiestrase-5 inhibitors in realaxation of phenylepherine precontracted rabbit corpus carvenosum strips[30]. In men, the administration of *L. meyenii* (Maca) at the dose of 1.5 and 3 g per individual for 4, 8 and 12 weeks stimulated sexual desire[31]. In impotent men with erectile dysfunction and taken three times daily, a capsule Korean Red Ginseng containing 1,000 mg showed an improvement of the erection in 66.6% of them[32].

ERECTILE DYSFUNCTION

Endocrine causes of erectile dysfunction: Many endocrine disorders can cause ED directly and indirectly including diabetes, hypogonadism, thyroid dysfunction, adrenal diseases, hyperprolactinaemia, obesity and iatrogenic causes. The hypothalamo-pitutary-testis axis is the most important endocrine system affecting male sexual function. The attribution of hypogonadism has been estimated from 2.1 to 21%. This discrepancy derives from differences in definition of ED, demographic characteristics of patients, diagnostic and inclusion criteria in different studies. As most endocrinologic causes of ED are treatable, every effort should be made to exclude potential hormonal aetiologies underlying ED at an early stage.

TESTOTERONE AND ERECTION

Testosterone and erection-studies in animals: In contrasts to the human data, numerous studies in animal models have demonstrated a direct role for testosterone in erection. In rats, testosterone enhances neurogenic and endothelial NO synthesis[33,34,35]. Testosterone has also shown to have an important role in maintaining cavernosal smooth muscle growth and functional integrity[36,37]. These effects are mediated by both testosterone and dihydrotestosterone but not oestradiol. In addition, reduction of intracavernosal pressure and blood flow after castration in rabbits was reversed by testosterone replacement[38]. The recent evidence is intriguing in that testosterone up regulates PDE-5, the enzyme that metabolizes cGMP, in rat and human caverenosal smooth muscle cells. This appears to counter its action on increasing NO synthesis.These data provides a plausible theoretical basis for combining testosterone treatment and PDE-5 inhibitors in patients who does not respond to high dose of PDE-5 inhibitors and have low normal or subnormal testosterone level. Two small-randomized placebo-controlled trials in humans provided preliminary evidence to support this view[39,40]. However, larger studies are needed to assess the long-term benefits of this combination therapy for ED.

Testosterone and erection in human: The presence of androgen receptors and 5-alpha reductase in human corpora cavernosa would potentially support a direct action of androgens on penile erection. However, early clinical studies have suggested that the action of testosterone on erection is predominantly mediated indirectly through central mechanisms such as sexual arousal and sleep (NPT). These studies, using penile circumference changes as the primary endpoint, have postulated a distinction between NPT, which is testosterone-dependent and erections in response to Visual Erotic Stimuli (VES), which appeared not to be influenced by testosterone deficiency or replacement. Similar studies on hypogonadal men using the Rigiscan which measured not only changes in penile circumference but also penile rigidity during sleep and in response to VES[41]. Testosterone treatment for 3 months induced a significant increase in penile circumference and rigidity during sleep (NPT) but also

a minor but significant improvement of both duration of erection and maximal rigidity in response to VES. More recently, using Penile Colour Duplex Ultrasound (P-CDU) to quantify pharmacologically (PDE-5 inhibitor)-induced erections, a relationship between low testosterone and impaired relaxation of cavernous smooth muscle has been demonstrated, regardless of age[42]. Studies have also shown that testosterone plays a role in the peripheral as well as central modulation of the erectile response. Fifteen untreated hypogonadal men (testosterone <200 ng dL^{-1}) 20 eugonadal controls were studied.

Nocturnal penile tumescence, pharmacologically induced erection assessed by P-CDU and visually stimulated erection were evaluated at baseline and after testosterone treatment. At baseline, there was a significant decrease in sleep related erections, P-CDU showed a partial erectile response to PDE-5 inhibitor and the VES response was impaired compared with controls. Administration of 3 mg apomorphine and 50 mg sildenafil had no influence on erectile function. However, 6 months of treatment with testosterone patch 5 mg daily induced normalization of testosterone levels, NPT, P-CDU parameters and of VES response with also a restoration of a normal response to pharmacological stimulation with apomorphine or sildenafil[42]. The use of newer methodologies to investigate erectile function in humans has added important new insights.These recent findings, in relation to rigidity necessitated a modification of our earlier formulation, which conceptualized spontaneous and sleep-related erections as androgen-dependent in contradistinction to erectile response to VES as androgen-independent. This appears now to be an oversimplification. It would appear that the erectile response to VES and possibly other potent external erotic stimuli may also be influenced by androgen-sensitive mechanisms but perhaps at a higher threshold level of testosterone compared with NPT.

PLANTS AND ERECTILE DYSFUNCTION

Plants with hormone stimulatory activity: It has been shown that testosterone and especially its active conversion product dihydrotestosterone stimulates erection by maintaining the nitric oxide level. This was also shown in castrated animals and men suffering from erection disorders in which the decrease of testosterone level is correlated with that of nitric oxide[43]. Several plants used traditionally in the treatment of male infertility showed stimulatory effects on testosterone production. The aqueous extract of *Hibiscus macranthus* and *Basella alba*, a plant mixture used traditionally to treat sexual asthenia has been shown to stimulate testosterone production at the dose of 720 mg kg^{-1} (equivalent whole plants) in male adult rats after 15 days of treatment[44]. It was later shown that the methanol extract of *B. alba* was the one possessing the androgenic properties in rat and bull Leydig cell culture (10 μg mL^{-1}) and also *in vivo* (1 mg kg^{-1} after 30 days of treatment) in adult male rats[45,46]. *Satureja khuzestanica* essential oil (75, 150 and 225 mg kg^{-1}) administered to adult male rats for 45 days increased serum concentrations of FSH and testosterone and the weights of testes, seminal vesicles and ventral prostate[47]. *Massularia acuminate* aqueous extract (250, 500 and 1,000 mg kg^{-1}) increased testis weight, serum concentrations of testosterone, LH, FSH and cholesterol in male rats after 7 and 21 days of treatment[48]. Similar androgenic activity was shown for a short period treatment in many reports: In male rats treated for 8 days with 400 mg kg^{-1} aqueous extract of *Mondia whitei* roots[49]. Aqueous extracts of *Zingiber officinale* (600 mg kg^{-1}), *Pentadiplandra brazzeana* (600 mg kg^{-1}) and fruits of *Piper guineense* (122.5 and 245 mg kg^{-1}) similarly increased the levels of testosterone, cholesterol, fructose and the activity of α-glucosidase in rats after eight days of treatment. Kamtchouing *et al.*[50] and Yakubu *et al.*[51] showed that the aqueous extract of *Fadogia agrestis* at the dose of 18, 50 and 100 mg kg^{-1} increased the serum concentration of testosterone in adult male rats after 1, 3 and 5 days of treatment. *T. terrestris* extract at the dose of 5, 7.5 and 10 mg kg^{-1} increased testosterone, dihydrotestosterone and dehydroepiandrosterone sulphate levels in primates (in acute treatment), rabbits and castrated rats after eight weeks of treatment[52].

SPERM ABNORMAILITIES

Medicinal plants and sperm abnormalities In rodents and other mammals: Several plant extracts have shown positive effects on sperm qualitative and quantitative parameters (azoospermia, oligospermia, asthenospermia, teratospermia). Administration of the ethanol extract of *Croton zambesicus* at the dose of 5 and 10 mg kg^{-1} *in vivo* increased the sperm number and motility but decreased malonic aldehyde levels and catalase activity in healthy mice after 5 days of treatment[53]. Korean ginseng (*P. ginseng*) administered at the dose of 1 g kg^{-1} for 56 days in male rats increased sperm count and motility, testis cAMP-responsive Element Modulator (CREM) mRNA and CREM protein[54]. Oral administration of *Nigella sativa* oil (0.5 mL day^{-1}) to healthy or hyperlipidemic rats for two months increased the weight of seminal vesicles, plasma testosterone level, sperm motility and count and decreased sperm abnormalities[55]. *Phoenix dactylifera* date palm pollen suspensions at the dose of 120 mg kg^{-1} for 35 days improved the sperm count, motility, morphology and DNA quality in healthy rats, with a concomitant increase in the weights of testes and epididymis[56]. Extract of *L. meyenii* (Maca) at the dose of 48 and 96 mg kg^{-1}

activated the onset and progression of spermatogenesis in healthy rats after 7, 14 and 21 days of treatment. In co-administration at the dose of 2.2 g daily^{-1} with lead acetate in rats for 19 days, it reduced the deleterious effect on daily sperm production caused by the chemical[57]. The juice of pomegranate (*Punica granatum*), given at the dose of 0.5 and 1 ml mL^{-1} a day for seven weeks to healthy rats, increased epididymal sperm concentration, sperm motility, spermatogenic cell density and diameter of seminiferous tubules and germinal cell layer thickness. It also improved antioxidant (decrease in malondialdehyde level and marked increases in glutathion (GSH), glutathione-peroxidase and catalase activities and vitamin C level) parameters[58]. The supplementation of the diet of subfertile (with poor normal sperm morphology-less than 70%) boars for two months with Cordyceps militaris mycelium at 10 g per day improved their sperm quality and quantity[59].

In humans: The aqueous extract of *Astragalus membranaceus* and *Acanthopanacis senticosi* at the concentration of 10 mg mL^{-1} increased the motility and the viability of infertile male sperm *in vitro*[60]. Decoctions of *Semen cuscutae*, *Rhizoma curculiginis* and *Radix morindae officinalis* improved sperm motility and the stabilization of sperm membranes *in vitro*, indicating that herbal decoctions may be beneficial in promoting sperm function for Intra-uterine Insemination (IUI) and *in vitro* Fertilization (IVF). Studies of Peng *et al.*[61], Xu *et al.*[62] and Fraser *et al.*[63] showed that 1, 10 and 100 nmol L^{-1} of genistein (a phytoestrogen) *in vitro* improved the capacitation and acrosome loss of normal human spermatozoa. Y virilin, a formulation of Indian medicinal plants, at a dose of one capsule twice a day increased sperm count and the conception incidence in oligospermic and asthenospermic men after six months of treatment in comparison with the placebo[64]. Meyenii (Maca) tablet (1.5 and 3 g per day for 4 months of treatment) increased sperm count and motility in healthy men while these effects were observed with in membranaceus extract (at 10 mg mL^{-1}) *in vitro*[65]. Speman (a formulation of several medicinal plants), at a dose of two tablets twice daily, increased sperm number and motility in oligospermic patients after six months of treatment[66]. Three months treatment of patients suffering from idiopathic infertility (sperm concentration between 5 and 15 million mL^{-1}) by a formulation of plants made up of *T. terrestris*, *Asparagus recemosus* and *Withania somniferea* increased semen volume, sperm count and motility[67].

Infertile men treated with a formulation of several Chinese medicinal plants (at 5 and 15 g in 1 L day^{-1}) for 1.5 and 6 months showed significant reduction in sperm disomy[68]. Kan Jan™ (mixture of *Andrographis paniculata* and *Acanthopanax senticosus*), at the dose of 1.578 g day^{-1} increased the number of spermatozoa in the whole ejaculate, the percentage of active (normokinetic) forms of spermatozoa and fertility indexes, together with a decrease in the percentage of inactive (diskinetic) forms of spermatozoa on the 9th day of the treatment in healthy men[69]. Powder of *Mucuna pruriens* seeds administered to infertile men who were under psychological stress at the dose of 5 g day^{-1} improved sperm count and motility, restored the levels of superoxide-dismutase (SOD), catalase, reduced GSH and ascorbic acid in seminal plasma after three months of treatment[70].

Effect of plant extracts on the levels of LH, FSH and GnRH in rodents: In rats, the aqueous extract of *Ruta chalepensis* leaves (0.5, 1 and 2 g kg^{-1} for 30 days of treatment) increased the weight of testes, epididymides and the testicular index. Also, it increased the sperm number, the sperm motility and viability as well as the levels of testosterone and FSH[71]. Polysaccharides of *Lycium barbarum* fruit extract (50, 100, 200 and 400 μg mL^{-1}) showed *in vitro* protective effects against DNA oxidative damage of mouse testicular cells induced by H_2O_2. At the dose of 10 mg kg^{-1}, it increased serum hormone levels (testosterone, LH, FSH) and accessory sexual organ weights in normal and hemicastrated rats after 14 and 21 days of treatment respectively. In hemi-castrated male rats, it also improved sperm quantity and qualities, shortened erection and mount latencies and increased mount frequency[72]. In diabetic rats, MTEC (a formulated herbal drug; consists of the aqueous-methanol extract of *Musa paradisiaca*, *Tamarin-dus indica*, *Eugenia jambolana* and *Coccinia indica*) given to animals at the dose of 600 mg kg^{-1} twice daily for 14 days increased animal body weight, testicular index, testosterone level and the sperm count and viability. It also increased the activity of 3- and 17-β-hydroxydehydrogenases and anti-oxidant parameters[73]. Recently, we found that *Peganum harmala* (50 mg kg^{-1}) extract *in vivo* exerts a protective antioxidant role as estrogens for the maintenance of the reproductive functions against the adverse effects of reactive oxygen species produced in large quantities in the aged testis of the rat after six months of treatment[74]. In fact, estrogens play essential role in the regulation of male reproductive function[75] (Table 1, 3).

Effect of plant extracts on the levels of LH, FSH and GnRH in humans: A 2-month clinical trial carried out in 202 infertile men (with abnormal semen profiles) using Shengjing pill, a Chinese formula of plant extracts, showed an improvement of sperm density, motility and viability. Serum concentrations of FSH, LH and testosterone were normalized by treatment and 78% of the 116 spouses conceived[76] (Table 2, 4).

Table 1: *In vitro* effects of medicinal plants on male reproductive functions in animals

Plant	Tissue/cells used	Dose	Duration of the treatment (min)	Obtained pharmacological effect	Refernce
Astragalus embranaceus	Spermatozoa suspension	10 mg mL^{-1}	15, 60, 180	Increases the viability and motility of spermatozoa	61
Acanthopanacis senticosi	Spermatozoa suspension	10 mg mL^{-1}	15, 60, 180	Increases the viability and motility of spermatozoa	61
Genistein	Spermatozoa suspension	1, 10, 100 nmol L^{-1}	30	Increases capacitation and the loss of acrosome	64

Table 2: *In vitro* effect of medicinal plants on male reproductive functions in humans

Plant	Tissue/cells used	Dose	Duration of the treatment	Obtained pharmacological effect	Reference
Epimedium revicornum	Rabbit corpus cavernosum	30, 300 and 1000 μg mL^{-1}	20 min	Relaxes corpus cavernosum	30
Lycium barbarum	Mouse testicular cells	50, 100, 200 and 400 μg mL^{-1}	1 h and 25 min	Protects DNA of testicular cells	73
Huperzia saururus	Guinea pig corpus cavernosum	10 mg mL^{-1}	5-7 min	Relaxes corpus cavernosum	80
Senecio eriophyton	Guinea pig corpus cavernosum	5 mg mL^{-1}	5-7 min	Relaxes corpus cavernosum	80
Satureja parvifolia	Guinea pig corpus cavernosum	10 μg mL^{-1}	5-7 min	Relaxes corpus cavernosum	80
Haplopappus rigidus	Guinea pig corpus cavernosum	10 μg mL^{-1}	5-7 min	Relaxes corpus cavernosum	80
Basella alba	Leydig cells	10 μg mL^{-1}	12 h	Stimulate testosterone level	46

Table 3: *In vivo* effect of medicinal plants on male reproductive functions in animals

Plant	Tissue/cells used	Dose	Duration of the treatment	Obtained pharmacological effect	Reference
Trichopus zeylanicus	Normal mice	200 mg kg^{-1}	1, 2 and 6 days	Increase mating performance	21
Vanda tessellata	Normal mice	50 and 200 mg kg^{-1}	1, 3 h	Increase mating performance	16
Turnera diffusa and *Pfaffia paniculata*	Sluggish Rat	1 mL kg^{-1}	2 h	Increase vigor and performance	17
Tribulus terrestris	Castrated rat	5 mg kg^{-1}	8 weeks	Stimulates libido	81
Terminala catappa	Normal male rat	1.5 g kg^{-1}400 mg kg^{-1}	7days	Increase vigor and performance	20
Butea frondonsa	Sexually active andinactive male rat	400 mg kg^{-1}	21 and 28 days	Increase vigor and performance	22
Myristica fragrans	Normal male rat	500 mg kg^{-1}	7 days	Increase vigor and performance	82
Syzgium aromaticum	Normal male rat	500 mg kg^{-1}	7 days	Increase vigor and performance	23
Epimedium koreanum	Normal male rat	300,750 mg kg^{-1}	10 days	Increase vigor and performance	24
Dactylorhiza hatagirea	Normal male rat	200 mg kg^{-1}	28 days	Increase vigor and performance and testosterone level	24
Montanoa tomentosa	Normal male rat	75 mg kg^{-1}	30 min.	Increase sexual arousal and mounting	83
Dracaena arborea	Castrated rats	100 mg kg^{-1}	7 and 14 days	Increase vigor and performance	50
Catha edulis	Normal male rat	100 mg kg^{-1}	15 days	Sexual motivation	28
Casimiroa edulis	Normal male rat	250 mg kg^{-1}	7 days	Increase vigor and performance	27
Ginkgo biloba	Normal male rat	50 mg kg^{-1}	14 and 28 days	Reduce ejaculation latency	26
Ruta chalepensis	Normal male rat	5, 1 and 2g kg^{-1}	30 days	Increase level of testosterone and FSH	72
Lycium barbarum	Normal and hemi castrated rats	10 mg kg^{-1}	14 and 21 days	Increase sexual behavior, hormones and weight of sexual organs	73
MTEC	Diabetic rats	600 mg kg^{-1}	14 days	Increase sperm characteristic, testosterone and body weight	74
Peganum harmala	Normal male rat	150 mg kg^{-1}	24 weeks	Antioxidant effect against reactive species	75
Basella alba	Normal male rat	10 mg kg^{-1}	4 weeks	Stimulate testosterone level	47
Mondia whitei	Normal male rat	400 mg kg^{-1}	8 days	Stimulate testosterone level	50
Zingiber officinale	Normal male rat	600 mg kg^{-1}	8 days	Increase testosterone and cholesterol	51
Pentadiplandra brazzeana	Normal male rat	600 mg kg^{-1}	8 days	Increase level of testosterone and cholesterol	51
Piper guineense	Normal male rat	122,245 mg kg^{-1}	8 days	Increase level of testosterone and cholesterol	84
Fidogia agrestis	Normal male rat	18, 50, 100 mg kg^{-1}	1, 3, 5 days	Increase testosteron levels	52
Satureja khuzestanica	Normal male rat	75, 150, 225 mg kg^{-1}	45 days	increase FSH and testosterone	48
Massularia accuminate	Normal male rat	250, 500 and 1000 mg kg^{-1}	7, 21 days	Increase testes weight level of FSH testosterone and colesterol	49
Tribulus terrestris	Primates rabbits and castrated rats	5, 7.5 and 10 mg kg^{-1}	8 week	Increase testosterone, DHT, DHEA sulphate	53
Panax quinquefolium	Normal male rat	100 mg kg^{-1}	28 days	Increase sexual vigor, performance decrease prolactin level	18
Eurycoma longifolia	Castrated rats	200, 400, 800 mg kg^{-1}	Twice daily for 10 days	Increase erection and mounting	19
Croton zambesicus	Normal male mice	5,10 mg kg^{-1}	5 days	Increase anti-oxidant parameters	54
Panax ginseng	Normal male rat	1 g kg^{-1}	56 days	Increase sperm count,motility testis. CREM mRNA and CREM protein	55
Nigella sativa	Healthy hyperlipidemic rats	0.5 mL day^{-1}	8 weeks	Increase weight of seminal vesicle, testosterone and sperm parameters	56
Phoenix dactylifera	Normal male rat	120 mg kg^{-1}	35 days	Increase sperm parameter, weight of testis and epidimysis	57
Lepidium meyenii	Normal male rat	48, 96 mg kg^{-1}	7, 14, 21 days	Activate the onset and progression of spermatogenesis	58
Punica granatum	Normal male rat	0.1 and 1 mL	7 weeks	Improve sperm quality	59
Cordyceps militaris	Subfertile boars	10 g day^{-1}	8 weeks	Improve sperm quantity and quality	60

Table 4: *In vivo* effects of medicinal plants on male human reproductive functions

Plant	Tissue/cells used	Dose	Duration of the treatment	Obtained pharmacological effect	Reference
Lepidium meyenii	Healthy men	1.5 and 3 g individual^{-1}	Oral route	4, 8 and 12 weeks	31
Korean Red Ginseng	Men with erectile dysfunction	1,000 mg 3 time daily	Oral route	3 months	32
Shengjing pill	Infertile men	-	Oral route	2 months	63
Y virilin	Oligospermic and asthenospermic men	1 capsule twice a day	Oral route	6 months	65
Lepidium meyenii	Healthy men	1 tablet (1.5 or 3 g) daily	Oral route	4 months	66
Speman	Oligospermic men	2 tablets twice daily	Oral route	6 months	67
Formulation of plants (*Tribulus terrestris, Asparagusrecemosus, Withania somniferea*)	Idiopathic infertile Men	-	Oral route	3 months	68
Formulation of Chinese medicinal plants	In infertile men	5 and 15 g /L day^{-1}	Oral route	6 months	69
Kan Jan™	Healthy men	1.578 g day^{-1}	Oral route	9 days	70
Mucuna pruriens	Infertile men under psychological stress	5 g day^{-1}	Oral route	3 months	71

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 contribute to the relaxation of the cavernous muscle and thus erection. Plant molecules such as sidenafil (Viagra®), yohimbine, L-citrulline, pyrano-isoflavones, berberine, papeverine, prostaglandin E1 and forskolin showed positive effects on erectile disorders[77]. Icariin, a compound isolated from *Epimedii herba* inhibited in a dose dependent manner, the activities of phosphodiesterase -4 and -5 *in vitro*[78]. Extracts of *Huperzia saururus* (10 mg mL^{-1}), *Senecio eriophyton* (5 mg mL^{-1}), *Satureja parvifolia* (10 mg mL^{-1}) and *Haplopappus rigidus* (10 mg mL^{-1}) showed *in vitro* relaxation effect on the guinea-pig corpus cavernosum for 5-7 min[79].

DISCUSSION

From the above paragraphs, many beneficial effects of medicinal plants on male reproductive function are associated with antioxidant effects[72,73,74]. This suggests that the potential of phytomedicines to improve male fertility is due to presence of antioxidants. Further-more, antioxidants have been shown to improve various processes (spermatogenesis, steroidogenesis) of male reproductive function[84,85].

Concerning differences in the duration of the administration of plant products in animals as well as in humans, it may be attributed to the variability in active principles and/or in their content in medicinal plants. In fact, we observed that it varies from one individual to another; some acting within minutes after ingestion while for other their effect appear after days or months[79]. The reduction of the dose of phytomedicines when studied is moved from rodents to humans (which is generally in month) may contribute to minimize cumulative adverse effects that should not be noted in short-term study. From the above pharmacological effects of plants, phytomedicines are used either single or in the formulation to treat various forms of male sexual dysfunctions. For those used single, some showed large spectrum of action. For example, *L. barbarum* due to its effect on hormone levels and on sperm parameters can be used in treating male asthenia and/or erectile dysfunction or sperm abnormalities. The multiple activities of plant products is crucial having in mind the interconnection amongst various clinical signs of male sexual dysfunctions. In human studies, plants are used generally in the form of formulations and the gathering of plants to treat male disorders have shown interesting effects on idiopathic infertility[66,67,68]. Medicinal plants have been evaluated on sexual desire, erection, mounting and ejaculation. These aspects of male reproductive function constitute the achievement of cellular events. For example, the secretion of sperm or ejaculation is a process including spermatogenesis (development of diploid germ cells to spermatozoa), maturation of spermatozoa in epididymis and secretion of the seminal fluid by prostate and seminal vesicles[16].

Results from the effects of medicinal plants on male fertility parameters would be more interesting if works on different cellular events and regulation of male reproduction function conducted take into account the duration of each of the events. The majority of studies hitherto undertaken were done with animals and few works were carried out on human subjects. Additionally, results obtained in certain clinical studies were controversial and sometimes not acceptable because of the insufficiency in the population study size and the method used to choose candidates. For example, Tempest *et al.*[68] showed a reduction in sperm disomy in men after treatment with the formulation of Chinese medicinal plants. However, this study was carried out on only six men and without placebo. One should encourage clinical and representative studies in order to complete the evaluation of the potential effects of medicinal plants in the treatment of male reproductive disorders.

From the reports presented in review, it is noted that study on medicinal plants do not followed a standard

guideline regarding the incubation time for *in vitro* studies (which vary from minutes to hours). The duration of treatment for *in vivo* studies in mammals, which vary from days to several months, does not take into account the duration of sperm production in the animals' models used. Considering the daily dose in *in vivo* studies, we observed that it vary from grams (1.5 to 15 g) in human studies to milligrams (5 mg generally) in rodents. It should be noted that despite the widespread of phytomedicines, the effect of a great proportion of plants used traditionally to treat male infertility and related disorders have not yet been scientifically assessed. Moreover, several medicinal plants remain in the secret of populations or tradipractitioners. The outcome of a better comprehension of the treatment of male reproductive disorders by medicinal plants would be a considerable even if only few plant products are finally effective and sure. It is therefore a great challenge to scientists to prove assertions generally made on medicinal plants and to define their standard use.

CONCLUSION

The importance of herbal products in the treatment of male infertility in developed countries as well as in developing countries is undeniable. Among medicinal plants in our knowledge on which scientific investigations have been conducted, those with clinical assessment in human subjects may already be advised to treat male reproductive problems. In individuals suffering from idiopathic infertility, therapy consists of many medicinal plants should be given only if proven in efficiency. In addition, clinical and representative studies should be encouraged in order to complete the evaluation of the potential effects of medicinal plants in the treatment of male reproductive disorders.

The treatment of male infertility has used and still uses phytomedicines for several reasons: (1) Improvement of natural fertility through the effect of phytomedicines on different compartments of the male reproductive system and (2) Use of phytomedicines to improve sperm parameters for New Reproductive Technologies (NRT). It is important for physicians treating male infertility to have some knowledge about the medicinal plants whose relevant scientific investigations have been done and how to combine this therapy with the modern one. Also, governments may set up guidelines and policies for the use of medicinal plants in their health system.

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