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REVIEW

Medicinal plants as potential male anti-infertility agents: a review

Les plantes médicinales dans le traitement de l'infertilité chez le mâle : mise au point

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Abstract For millions of couples, the inability to have a child is a personal tragedy and a large proportion of childless people are confronted with social stigmatization (blame) and personal frustration. Formerly assigned to women, infertility of a couple is nowadays equitably distributed between the two sexes. 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. Pharmacological activities of many of these plants have been shown in vitro using cells, in vivo (on laboratory animals) and human studies. For instance, extracts of *Panax ginseng*, *Panax quinquefolius* and *Lepidium meyenii* have shown positive effects on sexual desire; while extracts of *Astragalus membranaceus*, *Asparagus racemous*, *Withania somnifera*, *Andrographis paniculata* and *Acanthopanax senticosus* improved sperm parameters. 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. However, herbal products are still anarchically used in many regions and countries, and a great proportion of medicinal plants used traditionally to solve male reproductive disorders have not yet been scientifically evaluated. Therefore in this review, we have summarized most of the data dealing with the effects of plant extracts on mammalian reproductive functions.

Keywords Male infertility · Medicinal plants · Libido · Sexual asthenia · Erection · Sperm

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Résumé Pour des millions de couples à travers le monde, l'incapacité d'avoir un enfant est vécue comme une tragédie personnelle. Une large proportion d'entre eux est confrontée à des stigmatisations sociales dont les conséquences sont multiples. Jadis attribuées à la femme, les causes de l'infertilité d'un couple sont pratiquement équitablement partagées par des facteurs liés aux deux sexes. Parmi les différentes méthodes de traitement de l'infertilité masculine figurent les plantes médicinales qui sont utilisées parfois empiriquement sous forme d'extraits, de fractions ou de composés partiellement purifiés dans le traitement des difficultés de libido, d'asthénie sexuelle, d'érection et d'anomalies des paramètres spermatiques. Ces différents aspects d'anomalies sont évoqués dans cette revue en relation avec les extraits de plantes utilisés pour les normaliser. Les propriétés de plusieurs de ces plantes ont été démontrées au niveau cellulaire, in vivo sur des animaux de laboratoire et chez l'homme. Par exemple, les extraits de *Panax ginseng*, de *Panax quinquefolius* et de *Lepidium meyenii* ont présenté un effet bénéfique sur la libido, tandis que ceux d'*Astragalus membranaceus*, d'*Asparagus racemous*, de *Withania somnifera*, d'*Andrographis paniculata* et d'*Acanthopanax senticosus* améliorent qualitativement et quantitativement les paramètres spermatiques. Les plantes fournissent ainsi un potentiel de traitements abordables et accessibles pour beaucoup de couples infertiles. Cependant, les plantes médicinales sont encore anarchiquement utilisées dans de nombreuses régions, et une large proportion d'entre elles traditionnellement utilisées pour résoudre les difficultés liées à la fertilité masculine n'a pas jusqu'à lors fait l'objet d'investigations scientifiques.

Mots clés Infertilité mâle · Plantes médicinales · Libido · Asthénie sexuelle · Érection · Spermatozoïdes

Introduction

Around the world, one out of six couples trying to conceive has difficulties. Infertility is defined as one year of regular and unprotected intercourse without conception.

On evaluation, roughly 50% of affected couples have causal or associated male factors as a cause of infertility [1]. The couples suffering from infertility use concomitantly traditional medicine from natural plants and modern medicine as possibilities of treatment [2,3]. The use of medicinal plants in the treatment of diseases and dysfunctions goes back to several millennia and has considerably contributed to the development of pharmaceuticals since about 25% of modern drugs are derived from plants. In addition, up to 60% of the world's population uses herbal products for medical purposes [4,5]. Since two decades, the evaluation of natural materials as a source of potential drugs has been of resurgent interest in developing countries as well as in the developed ones. This growing interest for phytotherapy is due to several reasons namely; conventional medicine can be inefficient (ineffective therapy), abusive and/or incorrect use of synthetic drugs results in side effects and other problems, finding of the "natural", large therapeutic spectrum of plant products and their effectiveness in the treatment of chronic diseases, need for development of new drugs. Phytomedicines are dietary supplements with nutritional and revitalizing effects on the organism [5–8]. The World Health Organization encourages the use of medicinal plants, and invites researchers to define the rational use of medicinal plants as a source of new drugs [9].

Several extracts, fractions or molecules isolated from these plants are today largely used to treat or relieve different aspects of male infertility such as: absence of libido, sexual asthenia, erectile dysfunction, ejaculatory and relaxation dysfunctions, loss of orgasm, and sperm abnormalities. Although the causes of infertility in males are diverse, psychogenic and endocrinal disorders, vascular injuries and drug abuse are found as symptoms in infertile people [10]. Many in vitro, in vivo and clinical studies proved the empirical use of plants in the improvement of male fertility parameters. In this review, we focused on the use of medicinal plants in the treatment of male infertility symptoms (libido dysfunction, erectile and ejaculatory disorders, and sperm abnormalities) as well as the effectiveness of phytomedicines as a mode of treatment. Original papers and reviews published on google, pubmed and science direct from 1990 to 2008 were found using key words as: male infertility, incidence or prevalence of infertility, use of traditional medicine, androgenic activity of plant extracts, medicinal plants and male reproductive hormones, plant extract and sexual desire, aphrodisiac activity of plant extracts, plant extracts and sperm characteristics, etc. 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.

Plants in the treatment of male infertility

The inability to have a child is a personal tragedy for couples suffering from infertility [11]. These couples use both traditional medicine and modern therapies as treatment. In developing countries, traditional medicine particularly medicinal plants thanks to their accessibility, availability, and affordability are generally the first recourse of infertile couples [9]. Several plants are empirically used to treat different aspects of male infertility such as sexual asthenia, libido (sexual desire), erectile and ejaculatory disorders, and sperm abnormalities (azoospermia, oligospermia). The biological activities of many of these plants were confirmed by in vitro, and/or in vivo animal studies and in humans.

Plants and sexual desire (libido)

In rodents

The ethanolic extract of *Trichopus zeylanicus* at the dose of 200 mg/kg increased mating performances in male mice 1, 2 and 3 hours, and 6 days after administration [12]. A similar effect was noted with the ethanolic extract of *Vanda tessellata* flowers at the dose of 50 and 200 mg/kg, 1 and 3 hours after administration in male mice [13]. The lipidic extract from *Lepidium meyenii* enhanced sexual function of mice and rats, as evidenced by an increase in the number of complete intromissions and the number of sperm-positive females in normal mice, and a decrease in the latent period of erection in male rats with erectile dysfunction [14].

The extracts of *Turnera diffusa* and *Pfaffia paniculata* administrated to sexually sluggish/impotent rats at the dose of 1 ml/kg per 2 hours before testing, stimulated mating and ejaculatory performances, reduced mounting, intromission and ejaculatory latencies [15]. The extracts of *Tribulus terrestris* (5 mg/kg for eight weeks of treatment) stimulated rat libido (sexual desire) [16]. Roots of *Panax ginseng* or *Panax quinquefolius* (at the dose of 100 mg/kg for 28 days) increased physical strength and vitality – decrease of decrease in mount, intromission and ejaculation latencies and the plasma prolactin levels normal male rats [17]. Hyperprolactinemia is one of the factors associated with low androgen level in blood and erectile dysfunction [18]. Extract of *Eurycoma longifolia* given to castrated male rats at the dose of 200, 400 and 800 mg/kg twice daily for 10 days stimulated sexual arousal [19]. Seed extracts of *Terminala catappa* increased sexual vigor (mounting and intromission frequency) and sexual performance (intercopulatory interval) of rats at the dose of 1.5 g/kg after seven days of treatment [20]. The bark

extract of *Butea frondonsa* given at the dose of 400 mg/kg to male rats reduced mount, intromission, ejaculation latencies and post-ejaculatory interval after 21 and 28 days of treatment. It also increased mounting, intromission and ejaculatory frequencies [21]. The alcoholic extract of *Myristica fragrans* seeds (500 mg/kg for 7 days of treatment), the extract of *Syzygium aromaticum* flowers (500 mg/kg for 7 days of treatment) and the formulation of *Epimedium koreanum* (300 mg/kg and 750 mg/kg for 10 days of treatment) increased mating and intromission frequencies, decreased the intromission and post-ejaculatory latencies in male rats [22–24]. The aqueous root extract of *Dactylorhiza hatagirea* (200 mg/kg after 28 days of treatment) stimulated rat libido, mating and ejaculatory frequencies, increased testosterone level, and decreased the intromission and post-ejaculatory latencies [25]. The aqueous extract of *Montanoa tomentosa* (75 mg/kg) stimulated sexual arousal and increased mounting behavior in genitally anaesthetized animals, 30 minutes after administration [26].

Epimedium brevicornum Maxim (at the concentration of 30, 300 and 1,000 μg/ml for 20 minutes of incubation) has been shown in vitro to relax the corpus carvernosum smooth muscle precontratcted with phenylephrine in a concentration-dependent manner, increased the amount of cGMP product, and potentiated the phosphodiesterase-5 inhibitors in relaxation of phenylephrine precontracted rabbit corpus carvernosum strips [27]. The ethanol extract of *Dracaena arborea* (100 mg/kg for 7 and 14 days) increased erection, mounting and intromission frequencies in normal and castrated rats [28]. The extract of *Catha edulis* Foresk (khat) at the dose of 100 mg/kg reduced mounting and intromission latencies thereby enhancing sexual motivation/arousal in male rats after 15 days of treatment [29]. The aqueous extract of *Casimiroa edulis* at the dose of 250 mg/kg increased mounting and intromission frequencies, reduced mounting and intromission latencies and the post-ejaculatory interval in male rats after seven days of treatment [30]. *Ginkgo biloba* has been extensively studied and one of the properties of its extract (50 mg/kg for 14 or 28 days) is the increased ejaculatory frequency and reduced ejaculatory latency, while reducing serum prolactin levels in male rats [31].

In humans

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 [32]. 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 [33].

Plants and erectile function

Plants with hormone stimulatory activity

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 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 [34]. Polysaccharides of *Lycium barbarum* fruit extract (50, 100, 200 and 400 μg/ml) 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, 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 [35]. In diabetic rats, MTEC (a formulated herbal drug; consists of the aqueous-methanol extract of *Musa paradisiaca*, *Tamarindus indica*, *Eugenia jambolana* and *Coccinia indica*) given to animals at the dose of 600 mg/kg 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 antioxidant parameters [36]. Recently, we found that *Peganum harmala* (50 mg/kg) 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 [37]. In fact, estrogens play essential role in the regulation of male reproductive function [38,39].

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 [40].

Effect of plant extracts on testosterone level 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 [41]. 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 (equivalent whole plants) in male adult rats after 15 days of treatment [42]. 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) and also in vivo (1 mg/kg after 30 days of treatment) in adult male rats [43–45]. *Satureja khuzestanica* essential oil (75, 150 and 225 mg/kg) 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 [46]. *Massularia acuminate* aqueous extract (250, 500 and 1,000 mg/kg) increased testis weight, serum concentrations of testosterone, LH, FSH and cholesterol in male rats after 7 and 21 days of treatment [47]. Similar androgenic activity was shown for a short period treatment in many reports: in male rats treated for 8 days with 400 mg/kg aqueous extract of *Mondia whitei* roots [48]. Aqueous extracts of *Zingiber officinale* (600 mg/kg), *Pentadiplandra brazzeana* (600 mg/kg) and fruits of *Piper guineense* (122.5 and 245 mg/kg) similarly increased the levels of testosterone, cholesterol, fructose and the activity of α-glucosidase in rats after eight days of treatment [49,50]. Yakubu et al. [51] showed that the aqueous extract of *Fadogia agrestis* at the dose of 18, 50 and 100 mg/kg 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 increased testosterone, dihydrotestosterone and dehydroepiandrosterone sulphate levels in primates (in acute treatment), rabbits and castrated rats after eight weeks of treatment [52].

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 [53]. Icariin, a compound isolated from *Epimedii herba* inhibited in a dose dependent manner, the activities of phosphodiesterase-4 and -5 in vitro [54]. Extracts of *Huperzia saururus* (10 mg/ml), *Senecio eriophyton* (5 mg/ml), *Satureja parvifolia* (10 mg/ml) and *Haplopappus rigidus* (10 mg/ml) showed in vitro relaxation effect on the guinea-pig corpus cavernosum for 5–7 minutes [55].

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 in vivo increased the sperm number and motility, but decreased malonic aldehyde levels and catalase activity in healthy mice after five days of treatment [56]. Korean ginseng (*P. ginseng*) administered at the dose of 1 g/kg for 56 days in male rats increased sperm count and motility, testis cAMP-responsive element modulator (CREM) mRNA and CREM protein [57]. Oral administration of *Nigella sativa* oil (0.5 ml/day) 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 [58]. *Phoenix dactylifera* date palm pollen suspensions at the dose of 120 mg/kg 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 [59]. Extract of *L. meyenii* (Maca) at the dose of 48 and 96 mg/kg 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 with lead acetate in rats for 19 days, it reduced the deleterious effect on daily sperm production caused by the chemical [32,60]. The juice of pomegranate (*Punica granatum*), given at the dose of 0.5 and 1 ml/ml 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 [61]. 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 [62].

In humans

The aqueous extract of *Astragalus membranaceus* and *Acanthopanacis senticosi* at the concentration of 10 mg/ml increased the motility and the viability of infertile male sperm in vitro [63]. 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) [64]. Fraser et al. [65] showed that 1, 10 and 100 nmol/l 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 [66]. *L. 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 the *A. membranaceus* extract (at 10 mg/ml) extract in vitro [67,68]. 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 [69]. Three months treatment of patients suffering from idiopathic infertility (sperm concentration between 5 and 15 million/ml) by a formulation of plants made up of *T. terrestris*, *Asparagus recemosus* and *Withania somniferea* increased semen volume, sperm count and motility [70]. Infertile men treated with a formulation of several Chinese medicinal plants (at 5 and 15 g in 1 liter per day) for 1.5 and 6 months showed significant reduction in sperm disomy [71]. Kan Jan™ (mixture of *Andrographis paniculata* and *Acanthopanax senticosus*), at the dose of 1.578 g per day 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 [72]. Powder of *Mucuna pruriens* seeds administered to infertile men who were under psychological stress at the dose of 5 g per day 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 [73].

In vitro, in vivo studies in mammals and in humans are summarized in Tables 1–4 below.

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

Plant	Tissues/cells used	Dose	Duration of the treatment	Obtained pharmacologic effect	Authors
Epimedium brevicornum	Rabbit corpus cavernosum	30, 300 and 1,000 μg/ml	20 minutes	Relaxes the corpus cavernosum	[27]
Lycium barbarum	Mouse testicular cells	50, 100, 200 and 400 μg/ml	1 hour and 25 minutes	Protects of DNA of testicular cells	[35]
Huperzia saururus	Guinea pig corpus cavernosum	10 mg/ml	5–7 minutes	Relaxes of the corpus cavernosum	[55]
Senecio eriophyton	Guinea pig corpus cavernosum	5 mg/ml	5–7 minutes	Relaxes of the corpus cavernosum	[55]
Satureja parvifolia	Guinea pig corpus cavernosum	10 mg/ml	5–7 minutes	Relaxes of the corpus cavernosum	[55]
Haplopappus rigidus	Guinea pig corpus cavernosum	10 mg/ml	5–7 minutes	Relaxes of the corpus cavernosum	[55]
Basella alba	Leydig cells	10 μg/ml	12 hours	Stimulates testosterone level	[43]

Table 2 In vitro effects of medicinal plants on male reproductive functions in humans

Plant	Tissues/cells used	Dose	Duration of the treatment	Obtained pharmacologic effect	Authors
Astragalus membranaceus	Spermatozoa suspension	10 mg/ml	15, 60, 180 minutes	Increases the viability and motility of spermatozoa	[63]
Acanthopanacis senticosi	Spermatozoa suspension	10 mg/ml	15, 60, 180 minutes	Increases the viability and motility of spermatozoa	[63]
Genistein	Spermatozoa suspension	1, 10, 100 nmol/l	30 minutes	Increases capacitation and the loss of acrosome	[65]

Table 3 In vivo effects of medicinal plants on male mammal reproductive functions (excluding humans)

Plant	Animals	Dose	Mode of administration	Duration of the treatment	Obtained pharmacologic effect	Authors
Trichopus zeylanicus	Normal mice	200 mg/kg	Gavage	1, 2 and 6 days	Increases mating performances	[12]
Vanda tessellata	Normal mice	50, 200 mg/kg	Gavage	1, 3 hours	Increases mating performances	[13]
Turnera diffusa and Pfaffia paniculata	Sluggish/impotent rats	1 ml/kg	Gavage	2 hours	Increases sexual vigor and performance	[15]
Tribulus terrestris	Normal and castrated rats	5 mg/kg	Gavage	8 weeks	Stimulates libido	[16]
Terminala catappa	Normal male rats	1.5 g/kg	Gavage	7 days	Increases sexual vigor and performance	[20]
Butea frondonsa	Sexually active and inactive male rats	400 mg/kg	Gavage	21 and 28 days	Increases sexual vigor and performance	[21]
Myristica fragrans	Normal male rats	500 mg/kg	Gavage	7 days	Increases sexual vigor and performance	[23]
Syzygium aromaticum	Normal male rats	500 mg/kg	Gavage	7 days	Increases sexual vigor and performance	[22]
Epimedium koreanum	Normal male rats	300, 750 mg/kg	Gavage	10 days	Increases sexual vigor and performance	[24]
Dactylorhiza hatagirea	Normal male rats	200 mg/kg	Gavage	28 days	Increases sexual vigor and performance, and testosterone level	[25]
Montanoa tomentosa	Normal male rats	75 mg/kg	Gavage	30 minutes	Increases sexual arousal and mounting behavior	[26]
Dracaena arborea	Normal and castrated rats	100 mg/kg	Gavage	7 and 14 days	Increases sexual vigor and performance	[28]
Catha edulis	Normal male rats	100 mg/kg	Gavage	15 days	Enhances sexual motivation/arousal	[29]
Casimiroa edulis	Normal male rats	250 mg/kg	Gavage	7 days	Increases sexual vigor and performance	[30]
Ginkgo biloba	Normal male rats	50 mg/kg	Gavage	14 and 28 days	Reduces ejaculatory latency and serum prolactin level	[31]
Ruta chalepensis	Normal male rats	0.5, 1 and 2 g/kg	Gavage	30 days	Increases the sperm characteristics, and the levels of testosterone and FSH	[34]
Lycium barbarum	Normal and hemicastrated rats	10 mg/kg	Gavage	14 and 21 days	Increases sexual behavior, hormone levels and the weights of accessory sexual organs and superoxide dismutase activity	[35]
MTEC	Diabetic rats	600 mg/kg twice daily	Gavage	14 days	Increases animal body weight, testosterone level, and the sperm characteristics	[36]
Peganum harmala	Normal male rats	50 mg/kg	Gavage	6 months	Shows protective antioxidant effect against reactive oxygen species	[37]
Basella alba	Normal male rats	10 mg/kg	Gavage	1 month	Stimulates testosterone level	[45]
Mondia whitei	Normal male rats	400 mg/kg	Gavage	8 days	Stimulates testosterone level	[48]
Zingiber officinale	Normal male rats	600 mg/kg	Gavage	8 days	Increases the levels of testosterone and cholesterol	[49]

Pentadiplandra brazzeana	Normal male rats	600 mg/kg	Gavage	8 days	Increases the levels of testosterone and cholesterol	[49]
Piper guineense	Normal male rats	122.5, 245 mg/kg	Gavage	8 days	Increases the levels of testosterone and cholesterol	[50]
Fadogia agrestis	Normal male rats	18, 50 and 100 mg/kg	Gavage	1, 3 and 5 days	Increases testosterone level	[51]
Satureja khuzestanica	Normal male rats	75, 150 and 225 mg/kg	Gavage	45 days	Increases the levels of FSH and testosterone, and the weights of accessory sexual organs	[46]
Massularia acuminate	Normal male rats	250, 500 and 1,000 mg/kg	Gavage	7 and 21 days	Increases testis weight, the levels of testosterone, LH, FSH and cholesterol	[47]
Tribulus terrestris	Primates, rabbits and castrated rats	5, 7.5 and 10 mg/kg	Gavage	8 weeks	Increases the levels of testosterone, DHT and DHEA sulphate	[52]
Panax quinquefolium	Normal male rats	100 mg/kg	Gavage	28 days	Increases sexual vigor and performance, decreases the prolactin level	[17]
Eurycoma longifolia	Castrated male rats	200, 400 and 800 mg/kg	Gavage	Twice daily for 10 days	Increases erection and mounting	[19]
Croton zambesicus	Normal male mice	5 and 10 mg/kg	Gavage	5 days	Increases the sperm characteristics and antioxidant parameters	[56]
Panax ginseng	Normal male rats	1 g/kg	Gavage	56 days	Increases sperm count and motility, testis CREM mRNA and CREM protein	[57]
Nigella sativa	Healthy, hyperlipidemic rats	0.5 ml/day	Gavage	2 months	Increases the weight of seminal vesicles, plasma testosterone level, sperm parameters	[58]
Phoenix dactylifera	Normal male rats	120 mg/kg	Gavage	35 days	Increases the sperm parameters and the weights of testes and epididymis	[59]
Lepidium meyenii	Normal male rats	48, 96 mg/kg	Gavage	7, 14 and 21 days	Activates the onset and progression of spermatogenesis	[80]
3meyenii	Male rats treated with lead acetate	2.2 g/kg	Gavage	18 days	Reduces the deleterious effect of lead acetate on sperm	[60]
Punica granatum	Normal male rats	0.5 and 1 ml/ml per day	Gavage	7 weeks	Improves sperm and antioxidant parameters	[61]
Cordyceps militaris	Subfertile boars	10 g/day	Food supplements	2 months	Improves sperm quality and quantity	[62]

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

Plant	Subject	Dose	Mode of administration	Duration of the treatment	Obtained pharmacologic effect	Authors
Lepidium meyenii	Healthy men	1.5 and 3 g/ individual	Oral route	4, 8 and 12 weeks	Stimulates sexual desire	[32]
Korean Red Ginseng	Men with erectile dysfunction	1,000 mg 3 time daily	Oral route	3 months	Improved erection	[33]
Shengjing pill	Infertile men	–	Oral route	2 months	Improves sperm parameters, normalizes hormone level	[40]
Y virilin	Oligospermic and asthenospermic men	1 capsule twice a day	Oral route	6 months	Increases sperm count and the conception incidence	[66]
Lepidium meyenii	Healthy men	1 tablet (1.5 or 3 g) daily	Oral route	4 months	Increases sperm count and motility	[68]
Speman	Oligospermic men	2 tablets twice daily	Oral route	6 months	Increases sperm number and motility	[69]
Formulation of plants (*Tribulus terrestris*, *Asparagusrecemosus*, *Withania somniferea*)	Idiopathic infertile men	–	Oral route	3 months	Increases semen volume, count and motility	[70]
Formulation of Chinese medicinal plants	In infertile men	5 and 15 g in 1 liter per day	Oral route	1.5 weeks to 6 months	Reduces in sperm disomy	[71]
Kan Jan™	Healthy men	1.578 g/day	Oral route	9 days	Increases the sperm characteristics, fertility indexes, decreases inactive spermatozoa	[72]
Mucuna pruriens	Infertile men under psychological stress	5 g/day	Oral route	3 months	Improves sperm count and motility, restores antioxidant parameters	[73]

Discussion

From the above paragraphs, many beneficial effects of medicinal plants on male reproductive function are associated with antioxidant effects [35,37,56,61,73]. This suggests that the potential of phytomedicines to improve male fertility is due to presence of antioxidants. Furthermore, antioxidants have been shown to improve various processes (spermatogenesis, steroidogenesis) of male reproductive function [74–76].

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 [77]. 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 [40,66,69–71].

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 [13,78,79]. 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. [71] 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: improvement of natural fertility through the effect of phytomedicines on different compartments of the male reproductive system, 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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