

Aphrodisiac Herbal therapy for Erectile Dysfunction

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Abstract

Erectile dysfunction (ED) or male impotence is described as an inability to maintain penile erection primarily endothelial and neuronal dysfunction which is partly characterized by decreased production of nitric oxide (NO). Male impotence can be caused by androgen deficiency in aging men, atherosclerosis, diabetes mellitus, spinal cord injury, high level of cholesterol, hypertension, prostate surgery, prostate and heart disease, penis anatomical deformity, social and psychological conditions as unhappy marital relationship, depression, and stress. Aphrodisiac is a drink or food that arouse sexuality. It can be categorized into three groups according to their action mode as follows: increase sexual pleasure substances, increase libido substances (arousal, sexual desire), and increase sexual potency (erection effectiveness). Various extracts of medicinal plants and orally active drugs such as vardenafil, sildenafil, and tadalafil are used to increase arterial blood flow for treating (ED) in southwest Asia. Hence, this paper review focuses on medicinal plants used as aphrodisiacs for scientific validation and management of erectile dysfunction (ED).

Keywords: Aphrodisiacs, herbal plants, erectile dysfunction, penile erection

INTRODUCTION

Erectile dysfunction (ED) is a neurovascular condition that involves endothelium of the corpora cavernosal arterial blood vessels in the penis and indirectly to cardiovascular diseases. The causative factors that include ED are vascular, neurogenic, psychogenic, and hormonal factors mainly in 52% aging men 40 to 70 years of age, diabetes, hypertension, prostate and heart disease, obesity and due to certain medications, physical injury or anatomical deformity of the penis [1-4]. Other endocrine disorders are also responsible such as adrenal insufficiency, hypogonadism, low testosterone, hypercholesterolemia, atherosclerosis, and hypothyroidism [5]. Diabetes mellitus will be prevalent to 300 million by 2025 as in diabetes, structural changes, vasoconstrictors, attenuation of relaxation response factors (eg, nitric oxide NO) and vasoactive factors are increased in the corpus cavernosum [1, 6]. Thus, it is very important to treat diabetes-induced ED with medicinal plants. Medicinal plants have been anticipated to be one of the most valuable resources in therapeutic practices for human diseases [7-9]. Their therapeutic effect depends on their effective chemical constituents [10, 11].

ED can also be caused by psychological conditions and social problems such as stress, depression, and unhappy relationships that occurred in midlife [12]. It may also be prevalent in older men due to various age-related diseases. Some studies showed that age acts as an independent risk factor even after adjustment for other age-related diseases in severe ED. It requires more pain stimulation and a longer time to get an ejaculation in elderly individuals. Among health

care providers, testosterone replacement therapy for aging men has been practiced for many years but if the patient has no clinical signs of androgen deficiency then testosterone replacement therapy will have no clinical effect [13, 14].

Male Sexual Dysfunction

Male Sexual Dysfunction (MSD) is described as a repeated inability to achieve normal sexual intercourse and interference with a full sexual response cycle that leads to physical illness, anxiety, depression, psychological toll, and feeling of inadequacy mainly in males [2, 3]. It is more prevalent (about 10% between 17 and 96 years and 50% in men between 50 and 70 years of age) as psychological or physical health problems [15]. Male Sex disorders are classified into sexual function disorder, sexual orientation, and sexual behavior. Several factors are responsible to

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maintain normal sexual functions such as intracavernosal nitric oxide system, neural activity, vascular events, and androgens [16]. There are various causative factors for MSD that includes androgen deficiencies (hyperprolactinemia, testosterone deficiency), psychological disorders (performance anxiety, fear of sexual failure strained relationship, depression, and stress), chronic medical conditions, vascular insufficiency (atherosclerosis, venous leakage, diabetes, and hypertension), penile disease, (Peyronie's, priapism, smooth muscle dysfunction, and phimosis), neurological disorders (Parkinson's disease, Alzheimer's spinal cord, cerebral trauma, stroke, or nerve injury), pelvic surgery (to correct arterial or inflow disorder), systemic diseases (cardiac, renal pulmonary, hepatic, cancer, and post-organ transplant), drugs (anti-hypertensives, psychiatric medications, anti-depressants central agents, anti-androgens, and antiulcer), lifestyle (cigarette smoking, chronic alcohol abuse), and aging (decrease in hormonal level with age) [17-19].

Pathophysiology of ED and Priapism

Neurovascular mechanism of ED is complex and involves multiple factors such as neurotransmitters, hormones, vasodilators, arterial insufficiency as a result of atheromatous disease, psychogenic disturbance with failure to relax cavernous smooth muscle, damage to the parasympathetic nervous system, diabetes or following pelvic surgery such as radical prostatectomy, spinal cord injury, radical cystectomy or bowel resection and autonomic nervous system (sympathetic and parasympathetic) [19]. In the autonomic nervous system, cavernous nerves are unique because they do not release either acetylcholine (Ach) or norepinephrine as it relaxes corpora cavernosa smooth muscle via GMP (cGMP) cyclic that allows blood flow, cavernosal lacunar spaces, and erection [20]. Hence, norepinephrine is very important in the mediator process but it acts as a direct dilator of the smooth muscle of cavernosal bodies. Priapism is a condition associated with sickle-cell disease and leukemia and intracavernosal injection of drugs such as prostaglandin E1 which fails to subside after ejaculation [21]. Peyronie's disease causes a physical bend in the erect penis and also contributes to ED [22].

Aphrodisiac Herbs

1. *Pausinystalia johimbe* (yohimbe):

Yohimbine is an alkaloid derived from African tree *Pausinystalia johimbe* [23]. The plant is native to western and central Africa and is used as a pharmacological agent. Alpha-2 adrenergic receptor antagonist enhances norepinephrine release from the penile nerves by acting upon catecholamines from the synapse in the treatment of ED for over 70 years. In one clinical trial, purified alkaloid Yohimbine showed effect on small sample sizes which are methodologically weak for addressing psychogenic ED than placebo by using only 5 drops twice a day of a tincture (1:3 weight: volume ratio) routinely in patients treated for 2-4 weeks [24], and if patient's condition improves significantly, then psychogenic ED is better confirmed [1, 25]. At that point, nervine aphrodisiacs are

substituted, then tincture and upon long-term consumption, yohimbe is not recommended that can raise BP and anxiety. Yohimbine is contraindicated in post-traumatic panic disorder, stress disorder, and obsessive-compulsive disorder. Yohimbe and yohimbine also act as antidepressants that can enhance the efficacy of selective serotonin reuptake inhibitors and tricyclic antidepressant drugs [26].

2. *Crocus sativus* (saffron)

Crocus sativus (saffron) belongs to the family Iridaceae which is used as medicine for treating major depression. It acts as an endothelial protector. In one clinical trial, 20 Iranian men were given 200mg of saffron daily for 10 days and erectile rigidity, sexual function and baseline improved significantly. An open randomized crossover trial on 36 Iranian men with ED was performed. They were given either 30mg of saffron b.i.d. or sildenafil on demand for 12 weeks that resulted in no effect [27] whereas, in a double-blinded randomized trial, 15mg of saffron compared with fluoxetine b.i.d. to placebo for 4 weeks showed improved results in erectile function and libido without any significantly adverse effects [28]. Hence, saffron is helpful for treating psychogenic and antidepressant-induced ED as compared to arteriogenic ED [25, 26].

3. *Lepidium meyenii* (maca)

It is a native member of the Brassicaceae family cultivated in central Peruvian Andes. Hypocotyl and fused taproot are used for sexual tonification. Dried *L. meyenii* is rich in iodine, magnesium, iron, and amino acids. It has fertility-enhancing and aphrodisiac properties [29]. Based on randomized trials, maca has libido-enhancing properties that are favoured by indigenous people, but this herb is not suggested until more research on its characteristics is done. An American corporation wants to get patent by using extraction of plant but it was revoked due to a lot of work had been done in traditional knowledge and approved as a supplement to treat infertility [30].

4. *Rubus coreanus*

Rubus coreanus is mainly used in Korea for treating several diseases and grows in southern Korea [31]. Unripe *R. coreanus* has been used as a herbal medicine for centuries and crude *R. coreanus* is used for treating enuresis, asthma, impotence, spermatorrhea, and allergic diseases [32].

5. *Schisandra chinensis*

Schisandra chinensis is native to the forests of China, Korea, and Russia [33]. *Schisandra chinensis* berries have been used as an herbal medicine for ED, enuresis, night sweats, asthma, frequency, jaundice, wheezing, spontaneous sweating, cough, sputum, and diabetes. *Schisandra chinensis* extracts had shown a dose-dependent relaxation effect on vascular smooth muscle mediated by an endothelium-dependent norepinephrine pathway via dephosphorylation of the myosin light chain [32, 34].

6. *Epimedium koreanum*

Epimedium koreanum is used as a traditional herbal medicine in Korea as a potent enhancer of erectile function. Icariin is the main active component that has many biological effects as hormone regulation, improves cardiovascular function, anti-tumor activity, and modulation of immunological function [34, 35].

7. *Artemisia capillaris*

Artemisia capillaris has been used for treating liver cirrhosis, liver cancer, jaundice, and cholecystitis in Asian countries. Scoparone (6, 7-dimethoxycoumarin), the active component in *A. capillaris*, is used as antipyretic, diuretic, choleric agent, anti-inflammatory and for treatment of hepatitis and bilious disorders [36]. *Artemisia capillaris* has a significant relaxing effect on penile corpus cavernosum smooth muscle and increased sildenafil citrate-induced relaxation induced by phosphodiesterase type 5 inhibitors in the pre-contracted rabbit. NG-nitro-L-arginine-methyl ester and 1H-[1, 2, 4] oxadiazole [4, 3-a] quinoxaline-1-1 increased cAMP and cGMP levels in the perfusate and inhibited capillarisin relaxation [37, 38]. Thus, it can be used as a supplement or new medicine to treat patients with ED.

8. *Cuscuta chinensis*

Cuscuta chinensis Lam belongs to Convolvulaceae family and is used to treat osteoporosis, cardiovascular disease, senescence and to improve sexual functions in Chinese traditional medicine. *Cuscuta chinensis* has active constituents such as flavonoids, quinic acids, lignans and polysaccharides that are responsible for the pharmacological activities to relax corporal tension and increase cAMP and cGMP levels in penile corpus cavernosum tissue. Sildenafil citrate-induced relaxation can be improved by *C. chinensis* [1, 39, 40].

9. Garlic

Garlic has various medical and pharmacologic properties such as anticoagulative, hypoglycemic, antihypertensive and hypolipidemic properties. Chinese herb involves nitric oxide synthase (NOS)-NO-cyclic guanosine monophosphate (cGMP) pathway, testosterone level, adenosine monophosphate (cAMP), transforming growth factor β 1 (TGF β 1)/Smad2 pathway, oxidative stress as well as intracellular Ca^{2+} concentration [41, 42].

10. *Angelica sinensis*

Angelica sinensis is the dried root of angelica that increases blood volume and helps to relieve pain in TCM. *Angelica sinensis* solution helps to decrease NOS activity caused by cavernous nerve injury in rats [42, 43].

11. *Ligusticum chuanxiong* Hort

Ligusticum chuanxiong Hort is grown mainly in southwestern China. Vasoactive component isolated from *L. chuanxiong* is 'Ligustrazine', which primarily helps to alleviate pain, promotes blood flow, and relaxes cavernosal smooth muscle via mediating cAMP and cGMP [42, 44].

12. Folium Ginkgo Bilobae

The leaf of Ginkgoaceae plant is Folium Ginkgo Bilobae that mainly grows in China. EGb761 is extracted from Bilobae extract that has various effects such as neuroprotective and vasoprotective effects and also penile erection, and noncontact erection by enhancing dopamine contents in the brain. Bilobae extract (EGb761) can preserve the neural nitric oxide synthase (nNOS)-positive nerve fibers after cavernous nerve injury [42, 45, 46].

13. Common Cnidium Fruit:

Imperatorin and xanthotoxin are some Cnidium (*Cnidium monnieri*) Fruit extracts that help to treat ringworm, women's genitals swelling, and male impotence and relaxes corpus cavernosum with intact endothelium [42, 47]. Another major component of common cnidium fruit is Osthole that has a vasodilating effect, releases NO from endothelium by inhibiting phosphodiesterase, and relaxes corpus cavernosum on strips of rabbit [48].

14. *Tribulus terrestris*

Tribulus terrestris (zygophyllaceae) grows mainly in North China. The fruit of *Tribulus terrestris* helps to improve erectile function, increases androgen ability and does not enhance serum testosterone levels as an aphrodisiac property in many animal experiments [49, 50]. Hence, it needs to be investigated further for the pro-erectile property mechanism.

15. *Morinda officinalis*

Morinda officinalis is widely used in China for treating rheumatoid arthritis and impotence. A study done with *Morinda officinalis* extract (bajijiasu) showed pre-treatment by improving sexual performance and enhancing serum testosterone levels in male rats suffering from reproductive impairment [51]. In another study, oral administration of *Morinda officinalis* extracts increased sexual behavior and testosterone concentration of both normal and kidney-yang-deficient mice [27]. But, it needs further investigation for understanding the underlying mechanism.

16. Herba Cistanche

Herba Cistanche is the dried stem of *Cistanche* species that grows in extremely arid areas with intensive sunshine. Herbal Cistanche has various chemical constituents such as that shortens the erectile latency, enhances sex hormone levels and chinacoside that helps to relax Endothelium-dependent via NO-cGMP pathway in rats [28]. It is also helpful in chronic renal disease, impotence, and gynaecological diseases by acting as neuroprotection, antioxidation, and antiaging [52]. However, the role of Herba Cistanche for improvement of erectile function via this pathway needs further research.

17. Semen cuscuteae

The dried ripe seeds of *Cuscuta chinensis* Lam are Semen cuscuteae that has been used to treat impotence and seminal emission in China. kidney-yang deficiency symptoms can be

reversed by restoring the testosterone level present in *Semen cuscutae* as flavones [53].

18. *Lycium barbarum*

Lycium barbarum L extracts have polysaccharides that help in biological activities and for treating chronic diseases such as hepatitis, diabetes, hyperlipidemia, male infertility, promote nerve regeneration, and antioxidant properties that decrease penis erection latency in hemicastrated rats [42, 54].

19. Tetrandrine

Tetrandrine is a traditional Chinese medicine isolated from the root of *Stephania tetrandra* S Moore which has antipyretic, anti-inflammatory, and analgesic effects. Moreover, it is also helpful in the intracellularly stored Ca^{2+} release and inhibiting the extracellular Ca^{2+} influx in corpus cavernous smooth muscle cells [42, 55].

20. Neferine

Neferine, which is extracted from the embryo of lotus seeds, is very helpful in protecting vascular endothelium, it is antipyretic, sedative, hemostat agent in TCM, inhibit platelet aggregation, decrease VLDL oxidation (very low-density lipoprotein), and has a relaxant effect by Ca^{2+} release from intracellular calcium pool, inhibits the Ca^{2+} influx from extracellular matrix on rabbit corpus cavernosum, and increases cAMP concentration [42, 56].

21. *Kaempferia parviflora*

Kaempferia parviflora is found mainly in China, has an inhibitory activity against PDE5 by *K. parviflora* rhizome extracts (5,7-methoxy flavone) [42], and relaxes human cavernosum in vitro by voltage-dependent Ca^{2+} channel through 3,5,7,30,40-pentamethoxyflavone (PMF) [42, 57].

22. *Panax notoginseng*

Panax notoginseng grows in Guangxi and Yunnan province of China. The effective ingredients of *P. Notoginseng* are saponins that help in cardiovascular or cerebrovascular diseases. One study showed that its saponins improve erectile function by suppressing oxidative stress and enhancing Akt expression in diabetic ED rats by intraperitoneal injection for 4 weeks [58, 59]. Moreover, it helps to restore endothelial function by endothelial nitric oxide synthase (eNOS)/cGMP pathway in corpus cavernosum [60].

23. Berberine

Benzodioxoloquinolizine is extracted from rhizoma coptidis rootstalk that acts as Chinese herb such as phellodendron and radix berberidis. Berberine enhances eNOS mRNA expression that induces relaxation of corpus cavernosum and also helps to improve erectile function by antioxidant effect [61, 62].

24. Icariin

Icariin is the active component of traditional Chinese herb epimedium that helps in male impotence, erectile function by

various mechanisms that preserve the expression of NOS and inhibit PDE5 activity which increases the cGMP levels in hypertensive rats spontaneously [63]. It is also helpful in streptozotocin-induced diabetic rats that improve erectile function by down-regulating the TGF β 1/Smad2 signaling pathway in oral icariin treatment. It also enhances the circulating testosterone level with the damaged reproductive system in rats [64].

25. Yidiyin

Yidiyin, a Chinese herbal decoction helps in diabetic ED that enhances erectile function in diabetic patients and rats. On the International index of erectile function-5 (IIEF-5), both Yidiyin and hypoglycaemic drugs can increase patients' scores rather than using the hypoglycaemic drug alone [65]. Administration of Yidiyin in rats can improve erectile function through activating NOS-cGMP pathway. In clinical practice, some other formulas are also used to treat erectile dysfunction such as Xiaoyao pill, Yougui pill, and Fufangxuanju capsule [42]. Moreover, more related researches can be conducted in the future for investigating their mechanisms.

26. Oysters

Oysters are excellent aphrodisiacs, rich in taurine and zinc that have a cardioprotective effect, nerve transmission, and stimulate the male reproductive system [66, 67].

27. *Epimedium extract* (horny goat weed)

There are approximately 52 *Epimedium* species of herbaceous flowering plants, also known as rowdy lamb herb, bishop's hat or horny goat weed, that have been used to treat ED for over 2000 years [36, 68]. It relaxes the smooth muscle in the corpus cavernosum as icariin is able to inhibit PDE5 and PDE4 in vitro. Liu et al found that oral treatment with icariin elevated intracavernosal pressure, while Ma et al reported that *Epimedium* may have the potential to treat ED as icariin has been screened for pharmacological activity in vivo and vitro. It has also been reported that *Epimedium* may increase testosterone levels and thyroid hormone levels. However, to date, no human studies have been conducted [69].

28. *Phoenix dactylifera*

The date palm pollen (DPP) is used in traditional medicine against male infertility. The effect of *Phoenix dactylifera* pollen on sperm parameters and reproductive system of adult male rats was studied and the results indicated that the consumption of DPP suspensions improved the sperm count, motility, morphology, and DNA quality with a concomitant increase in the weights of testis and epididymis [70, 71]. Constituents in the date palm contain estradiol and flavonoid components that have positive effects on the sperm quality [72].

29. *Myristica fragrans*

Myristica fragrans, mainly named as nutmeg, which is commonly used as a spice and aphrodisiac herb, helps as an

alternative medicine for the management of stomachic and has carminative, tonic, nervous stimulant, aromatic, narcotic, astringent, hypolipidemic, antithrombotic, antifungal, antidysenteric, anti-inflammatory properties. It is used in Unani medicine for sexual disorders [7].

CONCLUSION

Herbal remedies are very useful to manage erectile dysfunction in a long history. Now they are used as a natural product for sustaining health worldwide due to less cost, decreased side-effects and its ready availability. Herbal plants are helpful in reducing intracellular Ca^{2+} concentration, elevating testosterone levels, increasing cAMP expression, and relieving oxidative stress. Therefore, the herbal plants with aphrodisiac potentials have increased the demand for screening medicinal plants that deal with various approaches to rectify erectile dysfunction. In this review, all medicinal plants have significant pharmacological activity. Moreover, active constituents from plants by identification and isolation may bring a dynamic change in the modern world. The use of allopathic drugs has various side-effects that limit the use of such drugs. Therefore, people are turning for alternative options as use medicinal plants with fewer side-effects in herbal medications for managing sexual dysfunctions.

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