REVIEW ARTICLE

Erectile dysfunction: A review and herbs used for its treatment

Ashwin Saxena, Pawan Prakash, Mayur Porwal, Neeraj Sissodia, Pravesh Sharma[1]
Department of Pharmaceutics, Vivek College of Technical Education, Bijnor, Uttar Pradesh, [1]Department of Pharmacology, Sanjeevan College of Pharmacy, Dausa, Rajasthan, India

Erectile dysfunction (ED) or male impotence is defined as the inability to have or sustain an erection long enough to have a meaningful sexual intercourse. ED tends to occur gradually until the night time or early morning erections cease altogether or are so flaccid that successful intercourse does not occur. Sexual health is an important determinant of quality of life. Today, millions of men, young and old, suffer from ED due to high levels of synthetic hormones (known as Xenoestrogens) in our diet/environment; nutritionally imbalanced diet resulting from poor quality of produces; and extremely low levels of testosterone. To overcome the problem of sexual (or) ED various natural aphrodisiac potentials are preferred. The present review discusses about aphrodisiac potential of plants, its biological source, common name, part used and references, which are helpful for researchers to develop new aphrodisiac formulations.

Key words: Aphrodisiac, erectile dysfunction, Phosphodiesterase

INTRODUCTION

Erectile dysfunction (ED), otherwise known as impotency, affects more than 30 million men each year; yet only about 200,000 seek help from a physician. Impotency remains largely unrecognized simply because most men do not discuss sexual problems with their doctors. In addition, many physicians do not ask or are uncomfortable dealing with the subject. ED is defined as the inability to sustain an erection well enough to perform intercourse and ejaculation.[1] While almost all men will experience some degree of sexual difficulty at one time or another, only those who are unable to have successful intercourse 75 percent of the time are considered impotent. Contrary to popular belief, ageing is not an inevitable cause of impotency. It does, however, take elderly men longer to develop erection and the force of ejaculation is diminished.[2]

Conventional medicine usually addresses ED issues by prescribing a drug regimen or surgery. Oral medications such as *Erecaid* or testosterone are rarely effective unless the condition is due to low testosterone levels. *Viagra*, *Cialis* and *Levitra*, which act to relax corpus cavernosal smooth muscle and facilitate erections, are not without their side-effects. Penile injections of Papaverine or Prostaglandin E1, which affect penile blood flow, can result in prolonged erections necessitating other drug therapy to counter act its effects. Additionally, the therapy can cause burning and eventual fibrosis of the penis. Lastly, malleable or inflatable prosthesis are used in severe cases, requiring surgical implantation. Such prosthesis often need to be surgically re-implanted, are uncomfortable and are subject to periodic failure.

ED can be broken down into primary and secondary impotency. Primary causes are rare and may be associated with low androgen levels, genetic defects and severe psycho-pathology. Secondary impotency is much more common and, as the name implies, results from something else such as diabetes, arteriosclerosis, neurological disorders, psychological issues, prolonged stress or previous surgery to the genitalia. Blood pressure medications and antidepressants may also lead to impotency, especially in the elderly.

Dietary factors largely ignored by conventional medicine, also fuel the problem as men with diets high in caffeine, sugar and alcohol experience more ED, as do men who smoke and use recreational drugs.[3] Psychological causes account for the majority of impotency complaints. A skilled and sensitive physician may often uncover this during an interview and suggest corrective measures.

Access this article online	
Quick Response Code:	Website: www.greenpharmacy.info
	DOI: 10.4103/0973-8258.102825

Address for correspondence: Prof. Ashwin Saxena, Department of Pharmaceutics, Vivek College of Technical Education, Bijnor, Uttar Pradesh, India. E-mail: ashwinpharma04@gmail.com
Received: 18-11-2011; **Accepted**: 21-02-2012

Men experience three types of erections:

- Reflexogenic erections are induced by tactile stimulation of the genitals. Men with lesions of the cervical or thoracic spinal cord (paraplegics) are still able to have this type of erection. A small number of men with complete transection of the spinal cord can also have erections, which are psychogenically induced.
- Psychogenic erections are induced by visual or memory associations.
- Nocturnal erections occur during rapid eye movement sleep and may take place anywhere from three to six times a night, lasting from 20 to 40 minutes. Generally, nocturnal erections begin with the onset of puberty and diminish in intensity, duration and frequency later in life. Erections during arousal and intercourse are often achieved as a combination of reflexogenic and psychogenic and a deficit in one or both areas can lead to impotency.

MALE SEXUAL DYSFUNCTION

Sex disorders of the male are classified into disorders of sexual function, sexual orientation and sexual behaviour. In general, several factors must work in harmony to maintain normal sexual function. Such factors include neural activity, vascular events, intracavernosal nitric oxide system and androgens.[4] Thus, malfunctioning of at least one of these could lead to sexual dysfunction of any kind. Sexual dysfunction in men refers to repeated inability to achieve normal sexual intercourse. It can also be viewed as disorders that interfere with a full sexual response cycle. These disorders make it difficult for a person to enjoy or to have sexual intercourse. While sexual dysfunction rarely threatens physical health, it can take a heavy psychological toll, bringing on depression, anxiety and debilitating feelings of inadequacy. Unfortunately, it is a problem often neglected by the healthcare team who strive more with the technical and more medically manageable aspects of the patient's illness.[5]

Sexual dysfunction is more prevalent in males than in females and thus, it is conventional to focus more on male sexual difficulties. It has been discovered that men between 17 and 96 years could suffer sexual dysfunction as a result of psychological or physical health problems. Generally, a prevalence of about 10% occurs across all ages. Because sexual dysfunction is an inevitable process of aging, the prevalence is over 50% in men between 50 and 70 years of age. As men age, the absolute number of Leydig cells decreases by about 40%, and the vigour of pulsatile lutenizing hormone release is dampened. In association with these events, free testosterone level also declines by approximately 1.2% per year. These have contributed in no small measure to prevalence of sexual dysfunction in the aged.

Male sexual dysfunction (MSD) could be caused by various factors. These include: Psychological disorders (performance anxiety, strained relationship, depression, stress, guilt and fear of sexual failure), androgen deficiencies (testosterone deficiency, hyperprolactinemia), chronic medical conditions (diabetes, hypertension, vascular insufficiency (atherosclerosis, venous leakage), penile disease (Peyronie's, priapism, phinosis, smooth muscle dysfunction), pelvic surgery (to correct arterial or inflow disorder), neurological disorders (Parkinson's disease, stroke, cerebral trauma, Alzheimer's spinal cord or nerve injury), drugs (side-effects) (anti-hypertensives, central agents, psychiatric medications, antiulcer, anti-depressants and anti-androgens), life style (chronic alcohol abuse, cigarette smoking), ageing (decrease in hormonal level with age) and systemic diseases (cardiac, hepatic, renal pulmonary, cancer, metabolic, post-organ transplant).[4]

Sexual dysfunction takes different forms in men. A dysfunction can be life-long and always present, acquired, situational, or generalized, occurring despite the situation. A man may have a sexual problem if he:

- Ejaculates before he or his partner desires
- Does not ejaculate, or experiences delayed ejaculation
- Is unable to have an erection sufficient for pleasurable intercourse
- Feels pains during intercourse
- Lacks or loses sexual desire.

MSD can be categorized as disorders of desire, disorders of orgasm, ED and disorders of ejaculation and failure of detumescence.

Disorders of Desire

Disorders of desire can involve either a deficient or compulsive desire for sexual activity. Dysfunctions that can occur during the desire phase include:

i. Hypoactive sexual desire (HSD) defined as persistently or recurrently deficient (or absent) sexual fantasy and desire for sexual activity leading to marked distress or interpersonal difficulty. It results in a complete or almost complete lack of desire to have any type of sexual relation.
ii. Compulsive sexual behaviours (CSBs) constitute a wide range of complex sexual behaviours that have strikingly repetitive, compelling or driven qualities. They usually manifest as obsessive-compulsive sexuality (e.g., excessive masturbation and promiscuity), excessive sex-seeking in association with affective disorders (e.g., major depression or mood disorders), addictive sexuality (e.g., attachment to another person, object, or sensation for sexual gratification to the exclusion of everything else) and sexual impulsivity (failure to resist an impulse or temptation for sexual behaviour that is

harmful to self or others such as exhibitionism, rape or child molestation).[6]

Erectile Dysfunction

This is a problem with sexual arousal. ED can be defined as the difficulty in achieving or maintaining an erection sufficient for sexual activity or penetration, at least 50% of the time, for a period of six months. It results in significant psychological, social and physical morbidity, and annihilates his essence of masculinity.[7]

Disorders of Ejaculation

There exists a spectrum of disorders of ejaculation ranging from mild premature to severely retard or absent ejaculation.

DIAGNOSIS

Epidemiology and Risk Factors

Erection is a neurovascular phenomenon under hormonal control. It includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism.

ED has been defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Although ED is a benign disorder, it affects physical and psychosocial health and has a significant impact on the quality of life (QoL) of sufferers and their partners and families.[8]

Epidemiology

Recent epidemiological data have shown a high prevalence and incidence of ED worldwide. The first large scale, community-based study of ED was the Massachusetts Male Aging Study (MMAS). The study reported an overall prevalence of 52% ED in non-institutionalized 40- to 70-year-old men in the Boston area in the USA; specific prevalences for minimal, moderate and complete ED were 17.2%, 25.2% and 9.6%, respectively. In the Cologne study of men aged 30-80 years old, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4%.[9] In the National Health and Social Life Survey (NHSLS), the prevalence of sexual dysfunctions (not specific ED) was 31%. The incidence rate of ED (new cases per 1000 men annually) was 26 in the MMAS study, 65.6 (mean follow-up of 2 years) in a Brazilian study and 19.2 (mean follow-up of 4.2 years) in a Dutch study. Differences between these studies can be explained by differences in methodology and in the ages and socio-economic status of the populations studied.

Risk factors

ED shares common risk factors with cardiovascular disease (e.g., lack of exercise, obesity, smoking, hypercholesterolaemia, metabolic syndrome), some of which can be modified. In the MMAS, men who began exercising in midlife had a 70% reduced risk for ED compared to sedentary men and a significantly lower incidence of ED over an 8-year follow-up period of regular exercise. A multicentre, randomised, open label study in obese men with moderate ED compared 2 years of intensive exercise and weight loss with a control group given general information about healthy food choices and exercise.[10] Significant improvements in body mass index (BMI) and physical activity scores, as well as in erectile function, were observed in the lifestyle intervention group. These changes were highly correlated with both weight loss and activity levels. However, it should be emphasized that controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in prevention or treatment of ED.

Post-radical Prostatectomy Erectile Dysfunction

Radical prostatectomy (RP) in any form (open, laparoscopic or robotic) is a widely performed procedure for patients with clinically localized prostate cancer (PCa) and a life expectancy of at least 10 years. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly important with the more frequent diagnosis of PCa in younger patients. Research has shown that about 25-75% of men experience post-operative ED. Post-RP ED is multifactorial. Cavernosal nerve injury induces pro-apoptotic (loss of smooth muscle) and pro-fibrotic (increase in collagen) factors within the corpora cavernosa. These changes may also be caused by poor oxygenation due to changes in the blood supply to the cavernosa. Because pre-operative potency is a major factor associated with the recovery of erectile function after surgery, patients being considered for a nerve-sparing radical prostatectomy (NSRP) should ideally be potent. It is also clear that cavernosal nerves must be preserved to ensure erectile function recovers after RP. In addition, the role of vascular insufficiency is of increasing interest in post-operative ED.[11]

Advances in basic and clinical research in ED during the past 15 years have led to the development of several new treatment options for ED, including new pharmacological agents for intracavernous, intraurethral, and, more recently, oral use. Treatment strategies have also changed following the poor outcomes seen in long-term follow-up of reconstructive vascular surgery.[12] An increasing number of men are seeking help for ED due to the great media interest in ED and the availability of effective and safe oral drug therapy. However, there are many physicians evaluating and treating ED without appropriate background knowledge and clinical experience. Thus, some men with ED may receive little or no evaluation before treatment and will therefore not receive treatment for any underlying

disease that may be causing their ED. Other men without ED may be requesting treatment simply to enhance their sexual performance. Given this situation, these European Association of Urology guidelines for the diagnosis and treatment of ED are a necessity [Figure 1].

Treatment of Erectile Dysfunction

The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone. ED may be associated with modifiable or reversible factors, including lifestyle or drug-related factors. These factors may be modified either before, or at the same time as, specific therapies are used.

As a rule, ED can be treated successfully with current treatment options, but cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients and hormonal causes (e.g., hypogonadism, hyperprolactinaemia), which can be potentially cured with specific treatment. Most men with ED will be treated with treatment options that are not cause-specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference.[13]

To counsel patients properly with ED, physicians must be fully informed of all treatment options. The assessment of treatment options must consider the effects on patient and partner satisfaction and other QoL factors as well as efficacy and safety.

Lifestyle Management in Erectile Dysfunction with Concomitant Risk Factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany ED treatment. The potential benefits of lifestyle changes may be particularly important in individuals with ED and specific comorbid cardiovascular or metabolic diseases, such as diabetes or hypertension.[14] Besides improving erectile function, aggressive lifestyle changes may also benefit overall cardiovascular and metabolic health, with recent studies supporting the potential of lifestyle intervention to benefit both ED and overall health. Although further studies are needed to make clear the role of lifestyle changes in the management of ED and related cardiovascular disease, lifestyle changes can be recommended alone or combined with Phosphodiesterease (PDE5) therapy. Some studies have suggested that the therapeutic effects of PDE5 inhibitors

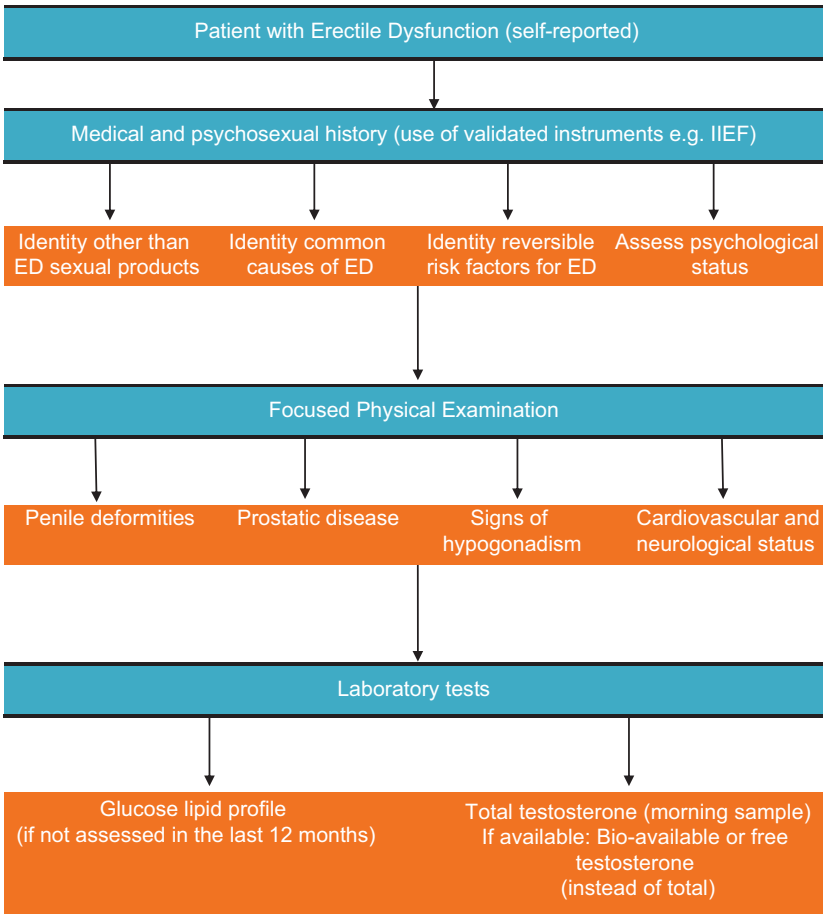

Figure 1: Managing ED: Implications for everyday clinical practice

may be enhanced when other comorbidities or risk factors are aggressively managed. However, these results have yet to be confirmed in well-controlled, long-term studies. Because of the success of pharmacological therapy for ED, clinicians need to provide specific evidence for the benefits of lifestyle change and hopefully future research will show this.

Erectile Dysfunction after Radical Prostatectomy

Use of pro-erectile drugs following RP is very important in achieving erectile function following surgery. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Historically, the treatment options for post-operative ED included intracavernous injections, urethral microsuppository, vacuum device therapy and penile implants. Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral compounds are not adequately effective or contraindicated for post-operative patients. The management of post-RP ED has been revolutionized by the advent of PDE5 inhibitors, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. At present, PDE5 inhibitors are the first-line choice of oral pharmacotherapy for post-RP ED in patients who have undergone a nerve-sparing (NS) surgical approach. The choice of PDE5 inhibitors as first-line treatment is controversial because the experience (surgical volume) of the surgeon is a key factor in preserving postoperative erectile function in addition to patient age and NS technique.[15] In fact, PDE5 inhibitors are most effective in patients who have undergone a rigorous NS procedure, which is more commonly performed by the largest-volume surgeons. The early use of a high dose of sildenafil after RP is associated with the preservation of smooth muscle within the human corpora cavernosa. Daily sildenafil also resulted in a greater return of spontaneous normal erectile function post RP compared to placebo following bilateral nerve-sparing RP (NSRP) in patients who were fully potent before surgery. The response rate to sildenafil treatment for ED after RP in different trials ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP.[16] The effectiveness of both tadalafil and vardenafil as on-demand treatment has also been evaluated in post-RP ED:

- A large multicentre trial in Europe and USA studied tadalafil in patients with ED following a bilateral NS procedure. Erectile function was improved in 71% of patients treated with tadalafil 20 mg versus 24% treated with placebo, while the rate of successful intercourse attempts was 52% with tadalafil 20 mg versus 26% with placebo
- Similarly, vardenafil has been tested in patients treated with ED following either an unilateral or bilateral NS procedure in a multicentre, prospective, placebo-controlled, randomised North American study.[17] Following bilateral NSRP, erectile function improved by 71% and 60% with vardenafil, 20 mg and 10 mg, respectively. An extended analysis of the same patients undergoing NSRP has underlined the benefit of vardenafil compared to placebo regarding intercourse satisfaction, hardness of erection, orgasmic function and overall satisfaction with sexual experience. A randomized, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on- demand and nightly dosing of vardenafil in men with ED following bilateral NSRP. In patients whose IIEF erectile function domain (IIEF-EF) score was ≥26 before surgery, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5 inhibitors in post-RP ED. Patients who do not respond to oral PDE5 inhibitors after NSRP should be treated with prophylactic intracorporeal alprostadil. A penile prosthesis remains a satisfactory approach for patients who do not respond to either oral or intracavernous pharmacotherapy or to a vacuum device.[18]

Curable Causes of Erectile Dysfunction

Hormonal causes

An endocrinologist's advice is essential for managing patients with hormonal abnormalities. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes, including a functional pituitary tumour resulting in hyperprolactinaemia. Testosterone replacement therapy (intramuscular, oral or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded. Testosterone replacement is contraindicated in men with a history of prostate carcinoma or with symptoms of prostatism. Before initiating testosterone replacement, a digital rectal examination (DRE) and serum Prostate-specific antigen test should be performed. Patients given androgen therapy should be monitored for clinical response and the development of hepatic or prostatic disease. There is no contraindication for testosterone therapy in men with coronary artery disease who have been properly diagnosed with hypogonadism and/or ED. However, the haematocrit level should be monitored and a dose adjustment of testosterone may be necessary, especially in congestive heart failure. Hormonal treatment is not always effective in the management of ED associated with hypogonadism.[19]

Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, surgical penile revascularization has a 60-70% long-term success rate. The lesion must be demonstrated by Duplex ultrasound and confirmed by penile pharmacoarteriography. Corporeal veno-occlusive dysfunction is a contraindication to

revascularization and must be excluded by dynamic infusion cavernosometry or cavernosography. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results.[20]

Psychosexual counselling and therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach. Psychosexual therapy takes time and has had variable results.

First-line Therapy

Oral pharmacotherapy

The PDE5 enzyme hydrolyzes cyclic guanosine monophosphate (cGMP) in the cavernosum tissue of the penis. Inhibition of PDE5 results in increased arterial blood flow leading to smooth muscle relaxation, vasodilatation and penile erection. Three potent selective PDE5 inhibitors have been approved by the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) for treatment of ED. They are not initiators of erection and require sexual stimulation to facilitate an erection.

Sildenafil

Sildenafil, launched in 1998, was the first PDE5 inhibitor available on the market. Efficacy is defined as an erection with rigidity sufficient for vaginal penetration. Sildenafil is effective from 30 to 60 min after administration. Its efficacy is reduced after a heavy fatty meal due to prolonged absorption. It is administered in 25, 50 and 100 mg doses. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects. Efficacy may be maintained for up to 12 h. Adverse events are generally mild in nature and self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of men taking 25, 50 and 100 mg of sildenafil, respectively, compared to 25% of men taking placebo. Sildenafil statistically improved patient scores in IIEF, sexual encounter profile 2 (SEP2), SEP3 and general assessment question (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. In diabetic patients, 66.6% reported improved erections (GAQ) and 63% successful intercourse attempts compared to 28.6% and 33% of men taking placebo, respectively.[21]

Tadalafil

Tadalafil, licenced for the treatment of ED as of February 2003, is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 h and is not affected by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. Adverse events are generally mild in nature, self-limited by continuous use. The drop-out rate due to adverse events is similar to placebo.[22]

Vardenafil

Vardenafil, commercially available as of March 2003, is effective from 30 min after administration. Its effect is reduced by a heavy fatty meal (>57% fat). It is administered in 5, 10 and 20 mg doses. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects. *In vitro,* it is 10-fold more potent than sildenafil, though this does not necessarily mean greater clinical efficacy. Adverse events are generally mild in nature and self-limited by continuous use, with a drop-out rate similar to placebo. After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil, respectively, compared with 30% of men taking placebo. Vardenafil statistically improved patient scores for IIEF, SEP2, SEP3 and GAQ and treatment satisfaction. Efficacy was confirmed in post-marketing studies. Vardenafil improved erections in difficult-to-treat subgroups. In diabetic patients, 72% reported improved erections (i.e., improved GAQ) compared to 13% of patients taking placebo and the final IIEF-EF score was 19 compared to 12.6 for placebo.[23]

Choice or Preference between the Different PDE5 Inhibitors

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil and vardenafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, possible disadvantages and how to use it.

On-demand or Chronic Use of PDE5 Inhibitors

Animal studies have shown that chronic use of PDE5 inhibitors improves or prevents significantly the intracavernous structure alterations due to age, diabetes or surgical damage. In humans, a randomised study (n=145) showed that daily tadalafil led to a significantly higher IIEFEF score and higher completion of successful intercourse attempts compared to on-demand tadalafil. Two major double-blind randomised studies, using daily 5 and 10 mg tadalafil for 12 weeks (n=268)[24] and daily 2.5 and 5 mg tadalafil for 24 weeks (n=286), showed that daily dosing was well tolerated and significantly improved erectile function. However, these studies lacked an on-demand treatment arm. An open-label extension was carried out of both studies in 234 patients for 1 year and 238 patients for 2 years. Tadalafil, 5 mg once daily, was

shown to be well tolerated and effective. Tadafil, 5 mg once daily, therefore provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. Nevertheless, in the 1-year open-label 5 mg tadalafil extension study followed by 4 weeks of wash-out, erectile function was not maintained after discontinuation of therapy in most patients (about 75%). A double-blind, placebo-controlled, multicentre, parallel-group study was conducted in 236 men with mild-to-moderate ED randomised to receive once-daily vardenafil 10 mg plus on-demand placebo for 12 or 24 weeks, or once-daily placebo plus on-demand vardenafil 10 mg for 24 weeks, followed by 4 weeks of wash-out. Despite preclinical evidence, the results suggested that once-daily dosing of vardenafil 10 mg does not offer any sustainable effect after cessation of treatment compared to on-demand administration in patients with mild-to-moderate ED. Other studies (open-label, randomised, cross-over studies with limited patient numbers) showed that chronic, but not on-demand, tadalafil treatment improved endothelial function with sustained effect after its discontinuation. This was confirmed in another study of chronic sildenafil in men with type 2 diabetes. Recently, in the first double-blind placebo-controlled study, enrolling 298 men with diabetes and ED for 12 weeks, once-daily tadalafil 2.5 mg and 5 mg was efficacious and well tolerated. This regimen provides an alternative to on-demand treatment for some diabetic men. However, when patients have the choice, it seems that they prefer on-demand rather than continuous therapy.[25]

Nitric Oxide Donors

Nitric oxide (NO) is a physiologic signal essential to penile erection, and disorders that reduce NO synthesis or release in the erectile tissue are commonly associated with erectile dysfunction. NO synthase (NOS) catalyzes production of NO from L-arginine.[26] While both constitutively expressed neuronal NOS (nNOS) and endothelial NOS (eNOS) isoforms mediate penile erection, nNOS is widely perceived to predominate in this role. Demonstration that blood-flow-dependent generation of NO involves phosphorylative activation of penile eNOS challenges conventional understanding of NO-dependent erectile mechanisms. Regulation of erectile function may not be mediated exclusively by neurally derived NO. Blood-flow-induced fluid shear stress in the penile vasculature stimulates phosphatidyl-inositol 3-kinase to phosphorylate protein kinase B, which in turn phosphorylates eNOS to generate NO. There are many herbal drugs that have been used by men for ED with varying degrees of success. Most potent herbal aphrodisiacs are available and have little or very little side effects [Table 1]. Thus, nNOS may initiate cavernosal tissue relaxation, while activated eNOS may facilitate attainment and maintenance of full erection.

1. L-arginine
2. Nitroglycerin paste
3. Paroxetine (NOS inhibitor)

Other Oral Agents

Several other drugs have been used in the treatment of ED with various mechanisms of action,[27] but today there is no place for these drugs in the treatment of ED.

Table 1: Herbal approaches in the treatment of erectile dysfunction

Name of plant	Common name	Family	Part used	Reference
Allium sativum L.	Garlic	Liliaceae	Bulb	[30]
Asparagus racemosus Willd.	Asparagus	Liliaceae	Root	[31]
Boerhavia diffusa L.	Punarnava	Nyctaginaceae	Root	[32]
Chlorophytum tuberosum Baker.	Safed musli	Liliaceae	Whole plant	[33]
Cocculs cardifolia Linn.	Guduchi	Menispermaceae	Stem, leaf, root	[34]
Fadogia agrestis Schweinf. Ex Heim	Black aphrodisiac	Rubiaceae	Stem	[35]
Myristica fragrans Houtt	Nutmeg	Myristicaceae	Seed	[36]
Panax ginseng	Ginseng	Araliaceae	Root	[37]
Turnera aphrodisiaca	Damiana	Trneraceae	Areal part	[38]
Withania somnifera Linn.	Ashwagandha	Solanaceae	Leaf, root	[39]
Pausinystalia yohimbe	Yohimbine	Rubiaceae	Bark	[40]
Ginkgo biloba	Ginkgo	Ginkgoaceae	Leaves, seeds	[41]
Tribulus terristeris	Caltrop	Zygophyllaceae	Seeds	[42-44]
Asphaltum bitumen	Shilajit	–	Pitch	[45]
Mucuna pruriens	Kapi kacchu	Fabaceae	Seed	[46]
Asparagus racemosus	Shatawari	Liliaceae	Root	[47]
Erythroxylem catuaba	Catuaba	Erythroxylaceae	Bark	[48]
Ipomoea digitata	Vidari kandha	Convolvulaceae	Root	[49]
Anacyclus pyrethrum	Akarakarabha	Compositae	Root	[50,51]
Allium tuberosum	Chienese chive	Zingiberaceae	Seed	[52,53]

- Yohimbine is a centrally and peripherally active alpha-2 adrenergic antagonist used as an aphrodisiac for almost a century.
- Delequamine is a more specific and selective alpha-2 adrenergic antagonist than yohimbine.
- Trazodone is a serotonin reuptake inhibitor (anti-depressant) associated with prolonged erections and priapism. It is also a non-selective alpha-adrenergic antagonist in the corporal smooth muscle cells.
- L-arginine is a nitric oxide donor and nalmefene/ naltrexone is an opioid-receptor antagonist.
- Red Korea ginseng is a formulation with an unknown mechanism of action (though it may possibly act as a nitric oxide donor).[28]
- Limaprost is an alprostadil derivative for oral use.
- An oral formulation of phentolamine (non-selective alpha-adrenergic antagonist) has undergone phase III clinical trials. Randomised trials have shown that yohimbine and trazodone have a similar efficacy to placebo in patients with organic causes of ED (99). Oral phentolamine had efficacy rates (erections sufficient for intercourse) of about 50%, but possible carcinogenesis in animal models stopped further development. Efficacy data on Red Korea ginseng suggested it might have a role in treatment of ED.[29] There are no efficacy data on the other drugs listed above.

CONCLUSION

Sexual function is an important component of quality of life and essential for subjective well being in humans. Sexual problems are widespread and adversely affect mood, well being and interpersonal functioning. Sexual problems are related to sexual desire and male erectile dysfunction. Successful treatment of sexual dysfunction may improve not only sexual relationships, but also the overall quality of life. Thus, this review has dealt with various approaches by which the screening of medicinal plants can be achieved. This is very important because of the side-effects associated with other treatment options and the readily availability of medicinal plants; now that the world is fast turning into the use of medicinal plants for managing sexual dysfunctions. Moreover, the side-effects occur through the use of allopathic drugs may limit the use of such drugs; therefore, the use of herbal drugs can be used as an alternative as there are less side effects in herbal medications.

REFERENCES

1. Ackerman M, Rajiah K, Veettil SK, Kumar S, Mathew EM. Impotence: Help for Erectile Dysfunction Patient Care. Victoria Island, Lagos: Scientific Research and Essays; 1994. p.22-56.
2. Mulligan T. Geriatric Sexual Dysfunction: A Rational Approach to a Sensitive Topic. 730 East Broad Street P.O. Box 980229 Richmond, VA 23298-0229: Virginia Geriatric Education Center; 1990.
3. Kahn J. Smoking May Increase Risk of Impotence Medical Tribune. Am J Epidemiol 1995;5:19.
4. Guay AT, Spark RF, Bansal S, Cunningham GR, Goodman NF, Nankin HR, *et al*. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: A couple's problem–2003 update. Endocr Pract 2003;9:77-95.
5. Salmon PH. Psychosexual dysfunction in chronic renal failure: An overview. Proc EDTNA. Pharmacogn Rev 1983;12:209-12.
6. Kaplan HS. Erotic obsession: Relationship to hypoactive sexual desire disorder and paraphilia. Am J Psychiatry 1996;153(7 Suppl):30-41.
7. Bosch RJ, Benard F, Aboseif SR, Stief CG, Lue TF, Tanagho EA. Penile detumescence: Characterization of three phases. J Urol 1991;146:867-71.
8. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61.
9. Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: Results of the 'Cologne Male Survey'. Int J Impot Res 2000;12:305-11.
10. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: Can lifestyle changes modify risk. Urology 2000;56:302-6.
11. Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, *et al*. Erectile dysfunction after radical prostatectomy: Hemodynamic profiles and their correlation with the recovery of erectile function. J Urol 2002;167:1371-5.
12. Wespes E, Schulman C. Venous impotence: Pathophysiology, diagnosis and treatment. J Urol 1993;149:1238-45.
13. Hatzichristou D, Rosen RC, Broderick G, Clayton A, Cuzin B, Derogatis L, *et al*. Clinical evaluation and management strategy for sexual dysfunction in men and women. J Sex Med 2004;1:49-57.
14. Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: Can lifestyle changes modify risk. Urology 2000;56:302-6.
15. Bianco F, Kattan M, Eastham J, Scardino PT, Mulhall JP. Surgeon and surgical volume as predictors of erectile function outcomes following radical prostatectomy. J Sex Med 2004;1:34.
16. Padma-Nathan H, McCullough AR, Levine LA, Lipschultz LI, Siegel R, Montorsi F, *et al*. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res 2008;20:479-86.
17. Brock G, Nehra A, Lipshultz LI, Karlin GS, Gleave M, Seger M, *et al*. Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. J Urol 2003;170:1278-83.
18. Montague DK. Penile prosthesis implantation for end-stage erectile dysfunction after radical prostatectomy. Rev Urol 2005;7 Suppl 2:S51-7.
19. Morales A, Heaton JP. Hormonal erectile dysfunction. Evaluation and management. Urol Clin North Am 2001;28:279-88.
20. Wespes E, Wildschutz T, Roumeguere T, Schulman CC. The place of surgery for vascular impotence in the third millennium. J Urol 2003;170:1284-6.
21. Stuckey BG, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F, *et al*., Deerochanawong C. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: Results of a randomized controlled trial. Diabetes Care 2003;26:279-84.
22. Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, *et al*. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: Results of integrated analyses. J Urol 2002;168:1332-6.
23. Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes:

A multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003;26:777-83.
24. Porst H, Giuliano F, Glina S, Ralph D, Casabé AR, Elion-Mboussa A, *et al*. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: Results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 2006;50:351-9.
25. Mirone V, Costa P, Damber JE, Holmes S, Moncada I, Van Ahlen H, *et al*. An evaluation of an alternative dosing regimen with tadalafil, 3 times/week, for men with erectile dysfunction: SURE study in 14 European countries. Eur Urol 2005;47:846-54; discussion 854.
26. Burnett AL. Novel nitric oxide signaling mechanisms regulate the erectile response. Int J Impot Res 2004;16 Suppl 1:S15-9.
27. Padma-Nathan H, Christ G, Adaikan G, Becher E, Brock G, Carrier S, *et al*. Pharmacotherapy for erectile dysfunction. J Sex Med 2004;1:128-40.
28. Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: A preliminary report. J Urol 2002;168:2070-3.
29. Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: A preliminary report. J Urol 2002;168:2070-3.
30. Joy PP, Thomas J, Mathew S, Skaria PB, Medicinal Plants. Thrissur, Kerala: Kerala Agricultural University, Aromatic and Medicinal Plants Research Station; 1998.
31. Satyavati GV, Raina MK, Sharma M, Medicinal Plants of India. Vol. 1. New Delhi: Ind. Council on Med. Res; 1976.
32. Jahan S, Rasool S, Khan MA, Ahmad M, Zafar M, Abbasi AM. Antifertility effects of ethanolic seed extract of Abrus precatorius L. on sperm production and DNA integrity in adult male mice. Indian J Tradit Knowl 2005;4:317-24.
33. Maiti S, Geetha KA. Horticulture Floriculture Medicinal and Aromatic Plants in India; 2007.
34. Prasanth PR, Kumar A. Ethno-medico botany of medicinal plants for the treatment of diabetic activity in Krishna district, Andhra Pradesh. Int J Pharm Res Dev 2008;9:1-9.
35. Yakubu MT, Adewmi MA, Oladiji TA. Male sexual dysfunction and methods used in assessing medicinal plants with aphrodisiac potentials. Res J Med Plants 2008;2:66-73.
36. Sumalatha K, Kumar SA, Lakshmi SM. Review on Natural Aphrodisiac potentials to treat Sexual dysfunction. Int J Pharm Ther 2010;1:10-8.
37. Nocerino E, Amato M, Izzo AA. The aphrodisiac and adaptogenic properties of ginseng. Fitoterapia 2000;71 Suppl 1:S1-5.
38. Kumar S, Madaan R, Sharma A. Evaluation of Aphrodisiac Activity of Turnera aphrodisiaca, Int J Pharmacognosy Phytochem Res 2009;1:1-4.
39. Singh KP, Kumar V, Tiwari KR, Sharma A, Rao CV, Singh RH. Medico-Ethnobotany of 'Chatara' Block of District Sonebhadra, Uttar Pradesh, India. Adv Biol Res 2010;4:65-80.
40. Fabricant SD, Farnsworth RN. The value of Plants Used in Traditional Medicine for Drug Discovery. Environ Health Perspect 2001;109 Suppl 1:69-75.
41. Welt K, Weiss J, Koch S, Fitzl G. Protective effects of Ginkgo biloba extract EGb 761 on the myocardium of experimentally diabetic rats. II. Ultrastructural and immunohistochemical investigation on microvessels and interstitium. Exp Toxicol Pathol 1999;51:213-22.
42. Available from: http://www.ayurhelp.com/plants/tribulus-terrestris.htm. [Last accessed on 2011 Nov 4].
43. Gauthaman K, Adaikan PG, Prasad RN. Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats. Life Sci 2002;71:1385-96.
44. Tomova M, Gyulemetova R. Steroidsapogenine, Tribulus terrestris Linn: A review article. Planta Med 1978;34:188-91.
45. Frotan MH, Acharya SB. Pharmacological studies of shilajit. Indian J Pharmacol 1984;16:45.
46. Parekar S. Estrogenic activity of Mucuna pruriens in swiss albino mice. Int Res J Pharm 2011;2:191-3.
47. Available from: http://www.science20.com/humboldt_fellow_and_science/blog/asparagus_racemosus_willd_has_medicinal_properties. [Last accessed on 2011 Nov 4].
48. Available from: http://thamilar-nalasevai.info/Media/healthcare/Male-Support_eng.pdf. [Last accessed on 2011 Nov 4].
49. Available from: http://www.himalayahealthcare.com/herbfinder/h_ipomoea.htm. [last accessed on 2011 Nov 4].
50. Available from: http://enchantingkerala.org/ayurveda/ayurvedic-medicinal plants/akkikaruka.php. [Last accessed on 2011 Nov 4].
51. Available from: http://users.skynet.be/bertram.zambiafoundation/Afbeeldingen/Literature_revue_Pyrethrum_root.pdf. [Last accessed on 2011 Nov 4].
52. Guohua H, Yanhua L, Rengang M, Dongzhi W, Zhengzhi M, Hua Z. Aphrodisiac properties of Allium tuberosum seeds extract. J Ethnopharmacol 2009;122:579-82.
53. Available from: http://www.inharmonyherbs.com/articles/95-herbal-aphrodisiacs.html. [Last accessed on 2011 Nov 4].

How to cite this article: Saxena A, Prakash P, Porwal M, Sissodia N, Sharma P. Erectile dysfunction: A review and herbs used for its treatment. Int J Green Pharm 2012;6:109-17.

Source of Support: Nil, **Conflict of Interest:** None declared.