

ERECTILE DYSFUNCTION AND ITS PHARMACOLOGY: AN OVERVIEW

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ABSTRACT

It has been estimated that currently over 150 million men worldwide suffer from erectile dysfunction (ED) and by 2025, the figure will increase beyond 322 millions. ED is the inability to achieve, and/or maintain penile erection sufficient for satisfactory sexual intercourse, and was previously regarded as the part of aging. It is associated with certain diseases and life style habits with a cause-effect relationship, including diabetes mellitus, hypertension, dyslipidemia, and cigarette smoking. Internationally, most of the men with ED fail to pursue treatment due to the complex nature of sexuality, taboos, cultural restrictions, and acceptance of ED as a normal sequel of aging. In this review, we discussed the physiology, diagnosis, and risk factors associated with ED and current treatment strategies for ED.

Keywords: Erectile dysfunction, Diabetes, Penile erection, Phosphodiesterase inhibitors.

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INTRODUCTION

Penile erection is an integrated part of male sexual behavior and is dependent on coordinated activities in the central and peripheral nervous systems, as well as on intact inter- and intra-cellular signaling pathways in the penis. Erectile dysfunction (ED) is next only to premature ejaculation in prevalence among male sexual problems [1]. However, it is known that medical practitioners often do not inquire about it in patients in whom it may not be the complaint [2]; even though, risk factors for it may be present; especially hypertension, use of antihypertensive drugs, diabetes mellitus, and smoking [3]. This situation is surprising because ED has a major negative impact on quality of life [4] and for this reason, it has been suggested that even if patients do not mention ED problems, physicians should not neglect to inquire about them [5]. It has been estimated that currently over 150 million men worldwide suffer from ED and by 2025, the figure will increase beyond 322 millions [6]. The prevalence of ED increases significantly with age, from approximately 10% between age 40 and 49 years to over 50% after age >70 years [7].

PHYSIOLOGY

Penile erection is a complex neurovascular event involving the interaction between different systems: The nervous system (central and peripheral) and the penile (arterial and trabecular) smooth muscle system. The tone of penile smooth muscle is a key determinant of the hemodynamic events that maintain penile flaccidity or allow erection. The cavernosal arteries supply blood to the corpora cavernosa of the penis (through the pudendal artery), whereas the emissary veins running through the tunica albuginea allow blood to flow out of the penis. In the flaccid penis, smooth muscle cells of corpora cavernosa are contracted and penile blood inflow is low. During erection, relaxation of trabecular smooth muscle results in an increased blood flow and pressure in the corpora cavernosa and an expansion of sinusoidal spaces (Fig. 1). The expanded corpora cavernosa cause mechanical compression of the emissary veins, restricting the venous outflow from the cavernosal spaces and facilitating an entrapment of blood in the cavernosal sinusoids. This blood engorgement finally results in penile rigidity [8].

Several neurotransmitters and endothelial factors have been shown to control erectile function by modulating the penile vasculature and

smooth muscle tone of corpora cavernosa [9]. The correct balance between relaxant and contractile factors is required to determine the functional state of the penis, finally resulting in a normal erectile function.

DIAGNOSIS AND RISK FACTORS

Diagnosis is best done by means of a detailed sexual history. The second is to ascertain the severity of the problem. This can be done objectively with questionnaires, for example, international index of erectile function (IIEF) [10] or it can be ascertained from the history. The third is to identify treatable conditions that may be relevant to the cause of the ED. Such conditions might include diabetes, hyperlipidemia, depression, hypertension, or hypogonadism (Table 1). Some of these conditions will be identified during history and examination, whereas others will require special investigations. The fourth objective is to identify patients who have causes of ED which might be amenable to specific treatment (Table 2) and also by physical examination (Table 3). The following sections will give a survey of the clinical studies that have addressed the possible role played by diabetes, cardiovascular diseases (CVD), obesity, and smoking in the development of ED.

DIABETES

Diabetes is associated with accelerated large vessel atherosclerosis and microvascular arterial disease, autonomic neuropathy, dyslipidemia, concomitant hypertension, and endothelial dysfunction. Diabetic men are 3 times as likely to develop ED as non-diabetic men. The cause is multifactorial, but most commonly reflects endothelial dysfunction and autonomic neuropathy. In a recent prevalence and risk factors analysis for ED using the IIEF-5, in men aged 20-80 years undergoing a health investigation, it was shown that 32.2% of men had ED according to the IIEF-5 and that the most important risk factor was diabetes [11]. ED in diabetes may be secondary to a neuropathic condition of the autonomic penile nerves. Indeed, it has been shown that there is a functional penile neuropathic condition of the cholinergic nerves in the corpus cavernosum of diabetic impotent patients that may be responsible for the ED.

This relationship between autonomic neuropathy and impotence in diabetes was studied in human tissue obtained during implantation

Table 1: Common organic risk factors for ED

Vascular disease	Atherosclerosis Hypertension Hyperlipidemia Diabetes mellitus
Neurological disease	Multiple sclerosis Spinal cord injury Pelvic nerve injury secondary to pelvic fracture
Endocrine disease	Hypogonadism Hyperprolactinemia Diabetes mellitus
Psychiatric and Psychological disease	Depression Anxiety disorders
Iatrogenic ED	Surgical damage to pelvic nerves (e.g., during radical prostatectomy) Radiotherapy for pelvic malignancy Drugs
Multifactorial problems	Renal failure Aging

ED: Erectile dysfunction

Table 2: Drugs that can cause erectile dysfunction

Antidepressants	Imipramine Doxepin Trazodone Isocarboxazid Desipramine Protryptiline Maprotiline Nortryptiline Clomipramine Tranylcypromine Amitriptyline Amoxapine Phenelzine
Antipsychotics	Chlorpromazine Thioridazine Pimozide Sulpiride Thiothixene Haloperidol Fluphenazine
Antihypertensives	Hydrochlorothiazide Reserpine Propranolol Guanadrel Spiroolattone Guanethidine Chlorthalidone Labetalol Alpha-methyl dopa Clonidine Guanabenz Atenolol
Drugs of abuse	Alcohol Cocaine Amphetamines
Anticonvulsants	Barbiturates Phenytoin Primidone Carbamazepine
Miscellaneous	Cimetidine Ketamine Metadone Digoxin Lithium Thiabendazole Clofibrate Acetazolamide Disulfiram Ketoconazole

of a penile prosthesis in 19 impotent diabetic and 15 non-diabetic patients. The functional status of penile cholinergic nerves was assessed by evaluating acetylcholine accumulation, synthesis, and release using tritiated choline. Tritiated choline accumulation and tritiated acetylcholine synthesis and release were significantly reduced in the corporeal tissue from diabetic patients compared to that from non-diabetic patients, and no differences were found between insulin-dependent and non-insulin-dependent diabetic patients [12].

CVD

There are several pieces of evidence in preclinical pharmacology and in clinical pharmacology that CVD represent a risk factor for ED. It is now generally accepted that the prevalence of CVD, such as ED, increases with age, but CVD by themselves are one of the major risk factor for ED. Overall, atherosclerotic vascular disease can account for almost 50% of the ED in men over 50 years of age. Heart disease and its associated risk factors, such as hypertension and low serum high density lipoprotein cholesterol, are significantly correlated with ED as demonstrated in the Massachusetts Male Aging study [13]. However, at present, there is an increasing interest in the possibility that ED represents an early sign of the existence of CVD, and that diagnosis of ED in an otherwise healthy patient could be considered an indication of a more systemic endothelial and vascular dysfunction.

Obesity

Healthy lifestyle factors are associated with maintenance of erectile function in men and there are several studies that have correlated life-style with ED. In an early study conducted in 1999 by Chung [14], ED was evaluated in 325 patients that were classified into 2 groups according to body weight: <120% and 120% of the ideal body weight. In this study, several erectile capacities were compared and a penile duplex ultrasonography analysis performed. In patients with obesity, there was a statistically significant decrease in the quality of residual erectile function measured as penile rigidity. Interestingly, 43% of the obese patients also displayed a significantly increased prevalence of vascular risk factors versus 30% in the non-obese, and 62% of the obese patients displayed a significant vascular impairment as assessed by duplex ultrasound versus 42% in the non-obese patients. However, when only the patients without any vascular risk factors were analyzed, no significant difference between the 2 groups was noted in the quality of residual erectile function and in the prevalence of penile vascular impairments ($p > 0.05$), suggesting that obesity in itself does not seem to be an underlying factor, but does impose a risk to vasculogenic impotence by promoting development of chronic vascular disease.

Smoking

It is important to point out that virtually every part of the body, including the urological system, is adversely affected by smoking. Smoking is a powerful predictor of ED; however, cessation may restore normal function. Cigarette smoke also exerts adverse effects on sperm motility and count [15]. At the molecular level, several changes associated with smoking have been documented in man. In particular, it has been shown that smoking causes an impaired penile flow. Cigarette smoking also interferes with the potency of intracavernous papaverine and prostaglandin E1 (PGE1), clearly indicating that smoking reduces not only endothelial function but also smooth muscle response [16].

TREATMENT

First-line therapy

Oral medications

The introduction of phosphodiesterase type 5 inhibitors (PDE5Is) in 1998, has clearly revolutionized the management of ED. Oral pharmacotherapy PDE5 is an enzyme that hydrolyzes cyclic guanosine monophosphate 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 are currently licensed with proven efficacy and safety for the treatment of ED.

Sildenafil

Sildenafil was the first PDE5 inhibitor and >20 million men have been treated in the 6 years since its launch. It is effective (erection with rigidity sufficient for vaginal penetration) after 30-60 minutes from administration [17]. Its efficacy is reduced after a heavy fatty meal (reduced, i.e., prolonged absorption). It is administered in doses of 25, 50, and 100 mg. The recommended starting dose is 50 mg and adapted according to the response and side effects. Efficacy may be maintained for up to 12 hrs [18].

Tadalafil

Tadalafil is effective from 30 minutes after administration, but its peak efficacy is expected in about 2 hrs [19]. Efficacy is maintained for up to 36 hrs [20]. Its efficacy is not influenced by food. It is administered in 10 and 20 mg doses. The recommended starting dose is 10 mg and is adapted according to the response and side effects.

Vardenafil

Vardenafil is effective after 30 minutes from administration. Its effect is reduced by a heavy fatty meal (>57% in fat). It is administered in 5, 10, and 20 mg doses [21]. The recommended starting dose is 10 mg and is adapted according to the response and side effects. In vitro, it is 10-fold more potent than sildenafil; however, this does not necessarily imply greater clinical efficacy [22]. Adverse events are generally mild in nature and self-limited by continuous use.

Contraindications

Concomitant (e.g., within 24 hrs for sildenafil and vardenafil, and 48 hrs for tadalafil) use of nitrate-containing medications (e.g., nitroglycerin, isosorbide dinitrate) is an absolute contraindication to PDE5Is use, as it can cause severe hypotension that can result in death. PDE5Is for patients who have recent serious cardiac events, poorly controlled hypertension, unstable angina or retinitis pigmentosa should be used with caution [23]. Coexisting cardiac conditions including stable coronary artery disease and heart failure do not pose higher risk of cardiac ischemia, coronary vasoconstriction or worsening of the hemodynamic profile on exertion [24,25].

Adverse events

Adverse events for all three PDE5Is are generally mild and well-tolerated. Common side effects are similar for all three PDE5Is (Table 4). These include headache, flushing, dyspepsia, and nasal congestion. Other side effects specific to individual drug include musculoskeletal pain (3-6% with tadalafil), changes in color perception and light sensitivity (sildenafil and vardenafil) [26]. These visual changes are due to crossover effects of the drugs on PDE6, an isoform of PDE in the retina. A significantly more severe visual adverse event recently associated with PDE5Is is non-arteritic ischemic optic neuropathy, known to be the most common acute optic neuropathy and ranks second only to glaucoma as a cause of acquired optic neuropathy that can lead to sudden blindness.

Data are from the European Medicine Evaluation Association statements on product characteristics.

Apomorphine

Apomorphine is a centrally acting drug (dopamine agonist, mainly D2) that improves erectile function by enhancing the natural central erectile signals that normally occur during sexual stimulation. It is administered sublingually on demand in 2 or 3 mg doses. Apomorphine has been approved for ED treatment in many countries but not in the United States. Efficacy rates (erections hard enough for intercourse) range from 28.5% to 55% [27]. Due to rapid absorption, 71% of erections are achieved within 20 minutes. The most common adverse events are nausea (7%), headache (6.8%), and dizziness (4.4%).

Topical pharmacotherapy

Several vasoactive drugs (2% nitroglycerin, 15-20% papaverine gel, and 2% minoxidil solution or gel) have been used for topical application

Table 3: Critical aspects of the physical examination

Genitalia	Size and shape of penis Abnormalities of the prepuce including phimosis Palpable plaque signifying Peyronie's disease Absent or small testes
Secondary sexual characteristics	Body habitus Gynaecomastia Appropriate hair distribution Body fat distribution
Vascular system	Blood pressure assessment

Table 4: Common adverse events of the three PDE5 inhibitors

Adverse event	Sildenafil (%)	Tadalafil (%)	Vardenafil (%)
Headache	12.80	14.50	16
Flushing	10.40	4.10	12
Dyspepsia	4.60	12.30	4
Nasal congestion	1.10	4.30	10
Dizziness	1.20	2.30	2
Abnormal vision	1.90	-	<2
Back pain	-	6.50	-
Myalgia	-	5.70	-

PDE5: Phosphodiesterase type 5

to the penis [28]. Adverse events include skin and glans erythema, burning sensation, allergic reactions, and side effects to the partner (hypotension, headache) due to absorption from the vagina.

Vacuum constriction device

This ED therapy functions via mechanical rather than pharmacological mean. It includes a plastic cylinder connecting to a vacuum-generating source powered manually or by battery. When placed on the penis, negative pressure provokes engorgement of blood to the sinusoidal tissue of the penile shaft and glands. An elastic ring is applied to the base of the penis to prevent egress of the trapped blood to enhance the rigidity for sexual activity. Despite several advantages such as no systemic side effects, high efficacy, low cost per treatment (after the initial expense for the device), the satisfaction rate of this device was only about 60-80% with a significant drop-out rate [29-31].

Second-line therapy

Intracavernosal injection

Available since the 1980s, intracavernosal injection with single or combination vasoactive agents (commonly alprostadil, papaverine, phentolamine, and moxidlyte) was once the most frequently used therapies for ED before the PDE5Is' era. Currently, for ED cases refractory PDE5Is (e.g. post-radical prostatectomy, severe diabetes or CVD) or when PDE5Is are contraindicated, intracavernosal injection remains an effective ED treatment, either alone or in conjunction with other ED therapies such as PDE5Is. Proper selection of candidates (e.g., adequate dexterity for needle manipulation, absence of bleeding diathesis, etc.) and proper education is the key to successful treatment with intracavernosal injection.

Transurethral medication

Alprostadil used in intracavernosal injection can be applied transurethrally at a higher dose (250-1000 µg) as a therapy for ED with a success rate of 40-69% [32-35]. Adverse events associated with transurethral alprostadil include urethral pain and injury, vasovagal reflex, hypotension, and priapism (<0.1%). Although it devoid the need of needle injection, its effectiveness is significantly lower than when administered intracavernously. The use of penile constriction ring at the base has been advocated to enhance the efficacy of transurethral

alprostadil and to reduce the risks of hemodynamic adverse events by slowing the rate of systemic absorption of the drug [36].

Testosterone replacement therapy

Androgens regulate erectile physiology via multiple mechanisms [37]. The decline in serum bio-available testosterone with aging can contribute to the severity of ED. When properly diagnosed and treated, testosterone replacement has been shown to be safe and effective in enhancing sexual desire and the efficacy of other forms of ED therapies [38,39]. Testosterone replacement can be administered transdermally, orally, intramuscularly or via buccal mucosa.

Penile prosthesis

The insertion of a penile prosthesis, which can be either a semirigid/malleable type made of silicone rubber with a central intertwined metallic core or hydraulic prosthesis that can be inflated or deflated through activation of scrotal pump controlling water flow from a suprapubic reservoir to the cylinders placed inside the corporal bodies of the penis, can virtually guarantee an erection for successful intercourse [40]. The surgical technique of penile prosthesis placement has been significantly modified and most experts can perform it with a single longitudinal incision through the ventral part of the penis as an outpatient procedure [41]. Large studies demonstrated a satisfaction rate >95% [42].

There is little interference in the orgasm, ejaculatory or urinary function, particularly with the hydraulic prosthesis. Mechanical failure of the prosthesis can occur, particularly with the hydraulic prosthesis, at a rate of 5-20% in the first 5 years [23]. Infection rate of penile prosthesis has been reduced in the recent years as a result of improved surgical techniques, use of prophylactic antibiotics and modification of the

prosthesis materials that allow for antibiotic impregnation and elution. It should be noted that placement of penile prosthesis is irreversible as the corporal tissue is permanently altered, making it not possible to achieve physiologic erection. Thus, candidates for this surgical therapy for ED should be carefully selected and counseled.

Sex therapy

Before 1970s, individual psychotherapy was the typical treatment for sexual dysfunction. Evidently, ED can be a cause and a consequence of psychosocial stress. Many of the approaches developed in the 1980s and 1990s are still currently in use. These include behavioral therapy, dual-sex therapy of Masters and Johnson, corporal approach, hypnotherapy, and group therapy. With the introduction of effective Pharmac therapies, particularly the PDE5Is, the use of sex therapy for ED has clearly declined worldwide. Sex therapy, however, still plays an important role for other forms of sexual dysfunction including premature ejaculation, desire, arousal and orgasm problems, and other less common disorders.

Some natural products in treatment of erectile-dysfunction activity

Despite the world-wide interest in Viagra and the influence it has had on the search for a natural product which can deal effectively with the problem of ED, no such breakthrough has become a reality. Herbal medicines are widely available and are often used because of the belief that they are a safe alternative to conventional medication.

Dehydroepiandrosterone (DHEA)

DHEA is the major secretory steroidal hormone of the adrenal gland and its isolation dates back to 1934. In a comprehensive study [43] of 17 hormones it was shown that only DHEA showed a strong inverse

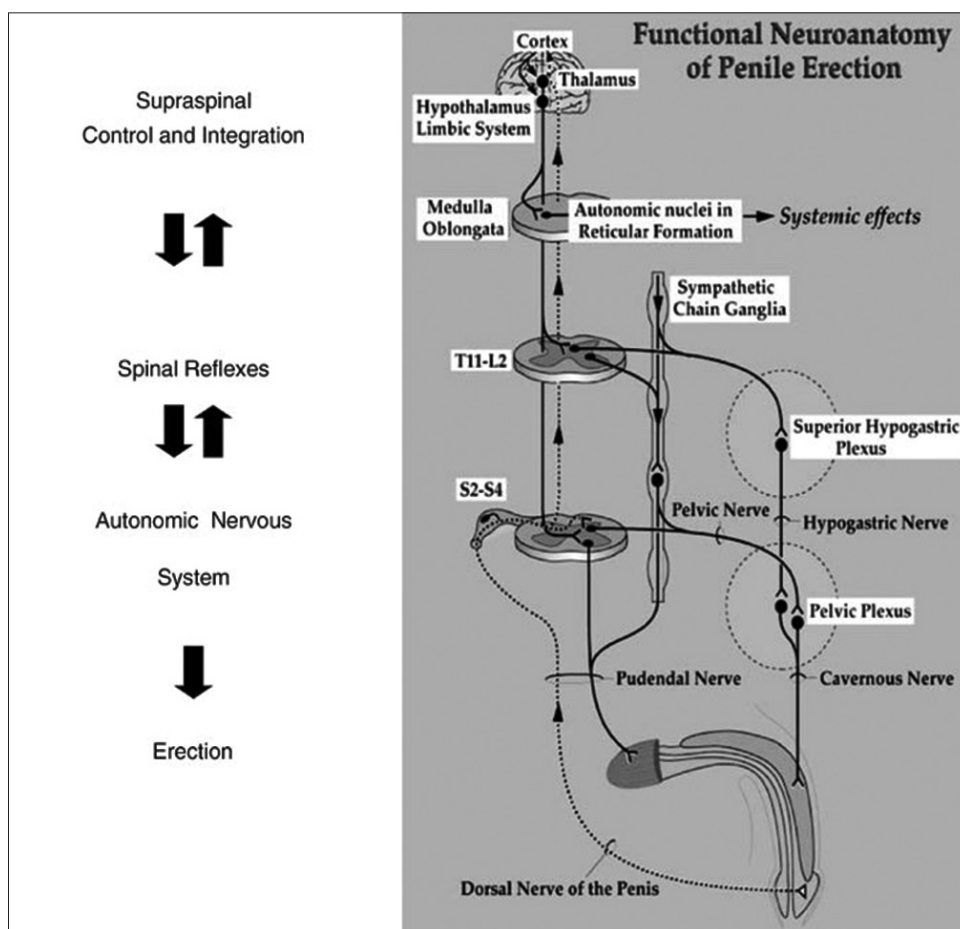


Fig. 1: Schematic representation of neurofunctional anatomy of penile erection

correlation to E-D. A more recent investigation [44], was carried out on 40 men of mean average age 56 to study the effects of DHEA on patients with ED. The results suggest that daily oral supplementation of the hormone produces a rise in serum levels of DHEA, concomitant with increase in sexual performance and satisfaction.

Yohimbine

Yohimbine is an indole alkaloid with α_2 -adrenergic blocking activity. It comes from the bark of *Corynanthe yohimbe* and its first isolation was in the early 1930s. The bark of the tree is traditionally used to enhance sexual prowess and virility. Renewed interest in yohimbine for E-D has prompted several new investigative (including chemical) trials. Indications are that in some cases yohimbine can improve sexual performance [45]. There are, however, indications of undesirable side-effects such as hypertension, anxiety, manic symptoms, and undesirable interactions with commonly used medications [46].

L-Citrulline

When L-citrulline [(N5-aminocarbonyl)-L-ornithine] is part of a formulation with calcium phosphate and other extenders, it is marketed under the trade name STIMULIN. The preparation is claimed to improve sexual stamina and ease E-D. The active ingredient in the formulation is L-citrulline which occurs naturally in watermelons. L-citrulline was first isolated in the 1930s, but its use as dietary supplement is of relatively recent origin. The activity of L-citrulline is attributed to its ability to release NO which, in turn, results in increased blood flow to the body, including the penis.

Berberine

Berberine is an alkaloid widely distributed in nature and occurs in Berberis plants such as *Berberis aristata* and *Berberis vulgaris* have undertaken a very detailed study on the relaxation of the corpus cavernosum and raised intravenous pressure by berberine in rabbit. For these tests, male New Zealand rabbits were used to obtain the corpus cavernosum tissue and the intravenous pressure change measured after intercavernosal injection of berberine. The overall results show that berberine possesses a relaxant effect on the rabbit corpus cavernosum tissue which is attributable to both endothelial-dependent and -independent properties.

Papaverine and prostaglandin E1

A combination of two natural products from *Papaver somniferum* and from sheep seminal vesicle tissue, respectively, has received renewed attention as a potential combination against male impotence [47]. It should be emphasized that both papaverine and prostaglandin E1 are recognized vasodilators. Research findings based on a clinical trial on 100 impotent male patients indicated that papaverine plus PGE1 was more effective than PGE1 alone. The procedure was not without its complications, however, and reinforced the earlier findings [48] that papaverine, phentolamine, and PGE1, as a combination gave rise to side effects such as priapism [49] (extended erection), local fibrosis, and pain.

Forskolin

The source in nature of the diterpene forskolin is the Indian herb *Coleus forskohlii*. It is of relatively recent origin (1977) and possesses vasodilatory and cardiostimulatory properties. In view of the cyclic adenosine monophosphate dependent effects produced by forskolin, it has found use as an agent for the treatment of congestive cardiomyopathy, glaucoma, and asthma. Forskolin has also been investigated as an intracavernosal vasoactive agent in the management of vasculogenic impotence. In in-vitro tests, forskolin and PGE1 alone caused concentration dependent relaxation. Combination of the two agents resulted in synergistic response [50]. Clinical investigation in 31 patients showed no adverse effects. Overall 61% of these reported improvement in rigidity of the penis and/or erection duration using a combination of forskolin, papaverine, phentolamine, and PGE1.

Tribulus terrestris

T. terrestris (devil's thorn) is used medicinally as a tonic for diarrhea and diseases of the throat and eyes. The work of Adimoelja [51] in Indonesia and Adaikan [52] in Singapore has drawn attention to a potential additional use of the extracts from *T. terrestris*. These researchers have presented evidence that protodioscin, a compound present in the *T. terrestris* extracts, can improve sexual desire and enhance erection. A commercial preparation of the *T. terrestris* preparation is sold under the trade name of Libilov.

Ginseng from Panax ginseng

The herbal tonic known commonly as ginseng enjoys extremely widespread use. Some chemical evidence supports the stimulatory action of the extract from *P. ginseng* or *Panax quinquefolius*, but the US Food and Drug Administration (FDA) have found no evidence of enhanced sexual experience resulting from its ingestion [51]. Earlier studies on Korean red ginseng [52] are in-line with the conclusions of the FDA and the authors state that "no complete remission of E-D was noted, but partial responses were reported." Root extracts of ginseng contain a variety of compounds such as steroids, peptides, triterpenoidal d-glucosides, and specifically panax sapogenin.

Lipidic extract from Lepidium meyenii (maca)

The plant *L. meyenii* belongs to the *Solanaceae* and has been known and used in the Andean mountains for 2000 years. While it has nutritional value it is also employed by the Andean Indians for enhancing fertility and sexual behavior in both sexes [53].

Eurycoma longifolia extracts

E. longifolia (*Simaroubaceae*), commonly called Tongkat Ali, is native to the jungle of Malaysia [54]. Antimalarial, cytotoxic, anti-ulcer, and anti-pyretic properties have been claimed for it over the years. Recently, it has figured prominently in the popular press on account of its reputed use to increase male virility. For this reason, several research groups have examined it for this property, notably using sexually experienced male rats [54]. It was found that rats treated with a specific dose of the extract, twice a day, displayed behavior of rats with enhanced sexual arousal [54].

Herbal medicine catuama

The combination of herbs, collectively known as "Catuama" in Brazil, consists of four plants cupana, *Trichilia catigua*, *Zingiber officinalis* and *Ptychopetalum olacoides* [55,56]. The individual components have also been used, separately, for centuries, for a variety of purposes (analgesic, antibacterial, cardiostimulant, purgative, and vasodilatory). However, it is the combination of the four that, in more recent times, has been promoted as an aphrodisiac.

CONCLUSION

Raising the penis from a dependent position to an erect position is a complex neurovascular event modulated by psychological factors and hormonal status. ED is an important public health problem affecting over half of all men ages 40-70. Sildenafil offers the first orally effective symptomatic treatment of ED. Oral sildenafil therapy, while effective in circumventing the cause of ED, provides only short-term symptomatic relief of the condition. Whole patient management of ED might also include psychological or relationship counseling, treatment of associated underlying chronic conditions, and the use of natural agents shown to improve derangements in penile endothelial L-arginine-NO activity. Truly, successful treatment strategies for ED must include the interplay between the mind and the nervous, vascular, and endocrine systems that results in erection.

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