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REVIEW ARTICLE

Comprehensive Perspectives for Erectile Dysfunction Pharmacotherapy: From Mechanism to Application

Haibao Zhang[1,2,3], Guodong Zhu[1,2,3,*], Haomin Ren[4], Wenbin Song[1,2,3] and Zhishang Yang[1,2,3]

[1]*Department of Urology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, P.R. China;* [2]*Oncology Research Lab, Key Laboratory of Environment and Genes Related to Diseases, Ministry of Education, Xi'an, P.R. China;* [3]*Key Laboratory for Tumor Precision Medicine of Shaanxi Province, Xi'an Jiaotong University, Xi'an, P.R. China;* [4]*Department of Anesthesiology and Perioperative Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, P.R. China*

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Abstract: In recent years, the incidence of erectile dysfunction (ED) has continued to rise worldwide. Since pharmacotherapy is still the most common and effective method for the treatment of ED at present, many methods and drugs have been designed or developed for the treatment of ED. Oral phosphodiesterase-5 inhibitors and androgen supplement therapy are currently the common therapeutics for ED; however, some patients have poor responses to these drugs because of the multiple pathogenic mechanisms of ED. Researchers are trying to find other treatment ways. On the one hand, many new strategies and concepts, such as targeted therapy, are also integrated into clinical or preclinical research; on the other hand, some combined therapies that have synergistic effects with a reduced dose of a single drug and less adverse effects are also developed. This review article summarized the efficacy of the latest first-line, second-line drugs and adjuvant therapies for the treatment of ED, as well as the application of comprehensive treatments, which will help doctors not only deeply understand the mechanism of ED but select the suitable therapeutics for those patients.

Keywords: Erectile dysfunction, pharmacotherapy, drugs, treatment, comprehensive, effect, sexual intimacy.

1. INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to attain a full erection or the inability to maintain a successful erection for sexual intimacy [1]. ED has become one of the most important diseases that plague men all over the world in recent years. About 150 million men suffer from ED at varying degrees, and by 2025, the number of patients will be larger [1-4]. ED has been gradually recognized by scholars as a disease with endangered healthy situations and mental affairs. The treatment of ED could be traced back to *The Yellow Emperor's Classic of Internal Medicine*, which was written in ancient China and considered as one of the classic books of Chinese Traditional Medicine [1]. In 1998, sildenafil became the first oral drug to be approved to treat patients with ED [5], which is an important event in history. Lots of current methods for the treatment of ED have arisen from basic research on the biochemical pathways and physiology in recent years.

Oral phosphodiesterase-5 inhibitors (PDE5is) are regarded as the first-line pharmacotherapy for the treatment of ED [1, 3, 5, 6]; however, in many medical conditions, lifestyle modifications were considered adjuncts to first-line therapy, which make indispensable effects in ED management [7, 8]. The main advantage of PDE5is result in the improvement of sexual performance but not libido. Despite advances, there is still a great need for more effective, long-lasting therapeutic drugs for the treatment of refractory ED. It is on the horizon that some innovative trends such as soluble guanylate cyclase (sGC) activators, stem cells and impulse magnetic-field therapy, which were still in the experimental stage, would be functioning properly in the penile tissue of men with ED [3, 4].

In fact, pharmacotherapy remains the most widely accepted treatment for ED not only for its significant effect, but it is also admissive for patients all over the world. The present review provides comprehensive per-

*Address correspondence to this author at the Department of Urology, the First Affiliated Hospital of Xi'an Jiaotong University, 277 West Yanta Road, Xi'an, 710061, P.R. China;
Tel: +86-029-85323661; E-mail: gdzhu@aliyun.com

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spectives for medication so as to assist sexual medicine physicians as well as urologic physicians.

2. EPIDEMIOLOGY

ED is a global problem as its prevalence is projected to increase in all continents. A study from Massachusetts found that 52% of men between 40 and 70 years old reported having some form of ED [9]. It is no doubt that ED is a major health problem for the aging population [10-12]. Thus, it seems that almost all men who live long enough would develop ED. Findings from several cross-sectional and longitudinal studies have shown the relationship between the increase of ED and diabetes mellitus Type II, cardiovascular disease, dyslipidemia, obstructive sleep apnea hypopnea syndrome, metabolic syndrome, some systemic diseases as well as general health, even local penile factors such as Peyronie's disease [1, 3, 13-16]. Above all, studies involved in both animal models and humans demonstrated that diabetes is regarded as the most common risk factor for ED, and patients with Type 2 diabetes are more likely to develop ED than those with Type 1 diabetes [1, 15]. Mental illnesses such as depression and anxiety disorders may also induce or aggravate ED caused by organic diseases [17-19].

Other studies have indicated that certain lifestyle and environmental factors, such as unhealthy diet, obesity, smoking, drinking, and absence of physical exercise, might also be assignable predictors of ED [13-15]. In some retrospective studies [18, 19], it has been found that changing bad lifestyles and increasing the amount of exercise moderately could reverse the harm of ED to some extent.

In summary, human penile ED is controlled by five factors, including local biological basis, systemic neuroendocrine regulation, behavioristics, personality cognition, and social, environmental factors. Lesions that occur in any of those levels can cause ED. At the same time, penile erection is subject to three-dimensional integration, including time, age, psychological and genetic factors.

3. PATHOGENESIS AND PATHOPHYSIOLOGY

Penile erection is a spinal reflex that is mediated by the interaction of three physiological systems [20]: central nervous system, peripheral nervous system, penile artery and cavernosal smooth muscle. The cavernous smooth muscle, smooth muscles of the arterial walls, and vascular endothelial cells play central roles in penile erection.

Some studies indicate that vascular endothelial dysfunction is one of the pathological bases of ED (Figs. **1** and **2**). Yavuzgil [21] and Foresta [22] found that compared with normal people, patients with ED showed obvious vascular endothelial damage and dysfunction. Vascular endothelial cell plays an important role in the regulation of coagulation and inflammation in the human body. When receiving stimulations, vascular endothelial cells secrete prostaglandin to regulate the cavernous smooth muscle to promote penile erection. Besides, vascular endothelial cells can also secrete a variety of active substances against thrombosis and maintain the internal pressure balance of blood vessels.

NO is a key neurotransmitter that maintains the relaxation of the smooth muscle of the corpus cavernosum. NO enters the cavernosal smooth muscle cells to stimulate soluble guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate. The cyclic guanosine monophosphate (cGMP) opens the calcium ion channel and allows calcium ions to enter the endoplasmic reticulum of the muscle cells, which leads to the relaxation of smooth muscles and entry of blood into the gap between the penile artery and the cavernous sinus, thereby forming a penile erection [23].

PDE5 degrades cGMP, causing contraction of the penile smooth muscle and weakening of the penis. The PDE5 inhibitor suppresses the degradation of cGMP by PDE5, allowing it to act as a second messenger in the penile artery and smooth muscle cells, and maintaining a long-lasting erection of the penis. These constitute the theoretical basis for first-line pharmacotherapy for ED.

4. PHARMACOTHERAPY

The combination of drugs currently in clinical use has offered some interesting possibilities, in a way reviving the approach that was prevalent 10 years ago with intracavernosal "trimixes" containing prostaglandin E2 (PGE2) as a stimulator of cAMP synthesis by binding to prostanoid receptors, papaverine as a nonspecific inhibitor of PDE increased both cAMP and cGMP levels, and phentolamine played as an adrenergic receptor blocker [24-27]. Although there was no clear advantage over single-drug treatment being obtained in small clinical trials, there were even some risks of undesirable side effects (priapism, hypotension), the concept is appealing since it was widely applied in other areas such as cancer and cardiovascular disease therapy [28-30]. It was based on the combination of drugs acting by different mechanisms with

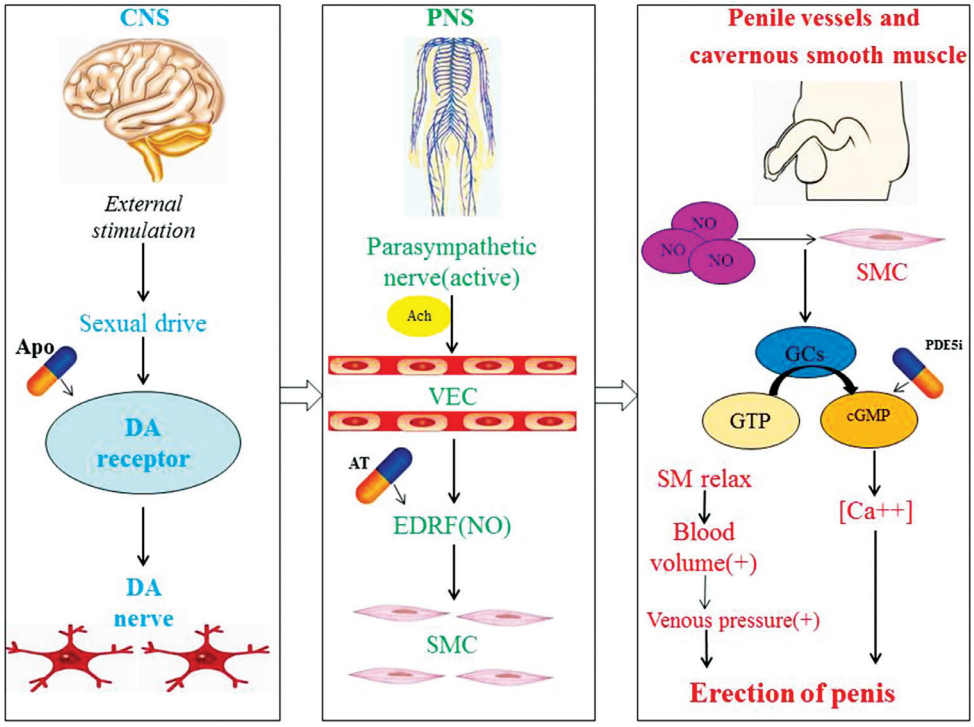


Fig. (1). PDE5 inhibitors degraded cGMP by inhibiting PDE5 for the second messenger to longer lasting in the penile artery and smooth muscle cells and maintaining a long erection of the penis. Androgen impaired NO synthase release, altered PDE5 expression and activity, impaired cavernous nerve function, penile vein occlusive disease. Apomorphine is a potent dopamine receptor agonist, and it plays a key role in the central nervous system to promote penile erection. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

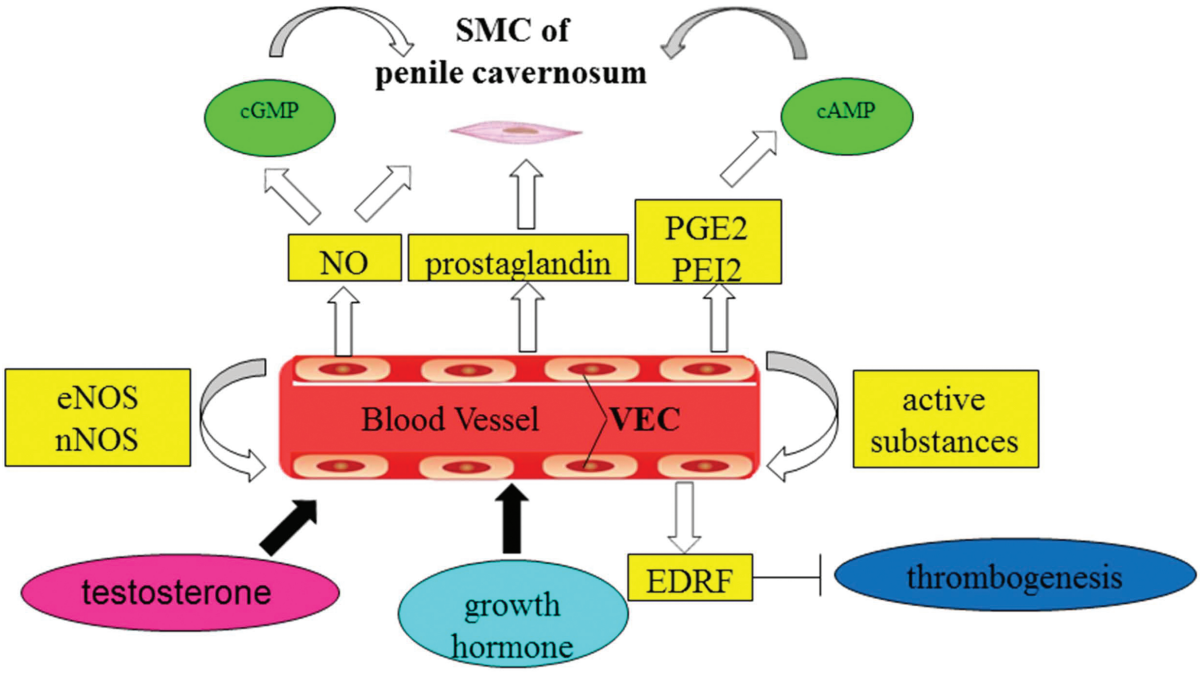


Fig. (2). Vascular endothelial cell plays a key role in ED. Vascular endothelial cells can release a variety of active substances that indirectly act on smooth muscle cells of penile cavernosum, and they can further regulate vascular pressure as well as inhibit thrombogenesis. Vascular endothelial cells can be also influenced by many hormones, which can form the feedback regulation loops. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

durable efficacy, and no overlapping adverse effects were observed. Such combinations may be oral or-sublingual but may also include oral/intracavernosal, and they involve cAMP and cGMP-dependent PDE inhibitors (sildenafil), which may act through both PKG and PKA activation [6-8, 18], with adrenergic receptor blockers (doxazosin), centrally acting dopamine receptor agonists (apomorphine) with PDE5 inhibitors or adrenergic receptor blockers, activators of guanylyl cyclase [31] and PDE5 inhibitors or NO donors [32].

PDE5 inhibitors are the breakthrough therapy in the treatment of ED. The PDE5 inhibitor selectively inhibits PDE5 and increases the amount of cGMP available for smooth-muscle relaxation, inducing vasodilatation, and increasing corporal blood flow and erection [1-3, 6-8]. Numerous studies [13-18, 28-33] have documented the efficacy, safety and tolerability of the competitive on-demand PDE5 inhibitor drugs sildenafil (Viagra, Pfizer, Inc., New York, NY, USA), tadalafil (Cialis, Eli Lily and Company, Indianapolis, IN, USA) and vardenafil (Levitra, Bayer Schering, Pharma AG, Leverkusen, Germany), and daily dosing of tadalafil in the treatment of ED in a wide range of patients, including those with hypertension, diabetes, spinal cord injury, other concomitant medical conditions and in those patients taking a wide variety of medications. The overall efficacy for the different PDE5 inhibitors appeared similar, with 65-70% of men achieving completion of sexual intercourse [24]. Efficacy is related to the extent and severity of ED, with significantly reduced efficacy demonstrated in patients with severe vasculogenic ED [31, 32], diabetic ED [28, 31] and post-radical prostatectomy ED [16, 25-27, 34]. Food high in fat reduces the absorption of sildenafil and vardenafil but does not affect the rate or extent of absorption of tadalafil [30-33]. The mean time to maximum plasma concentration of sildenafil and vardenafil was 1 hour and for tadalafil was 2 hours, while the half-lives of sildenafil and vardenafil are 4-5 hours and that of tadalafil is 17.5 hours [32].

PDE5 inhibitor drugs are contraindicated in patients taking aerosol, tablet or topical short-term or long-acting organic nitrates, such as nitroglycerin or isosorbide dinitrate. PDE5 inhibitors have been shown to cause greater decreases in blood pressure in some patients on organic nitrates [26, 28, 29]. Currently, there was no evidence of any direct deleterious effect on myocardium, and there was an increasing body of evidence to support the concept that PDE5 inhibitors improved endothelial function and, therefore, were likely to be cardioprotective.

4.1. Conventional Therapies

4.1.1. PDE5 Inhibitors

PDE5 inhibitors were approved as effective drugs by the European Medicines Agency for the treatment of ED [1, 3]. They are not the initiators of erections and need to be given sexual stimulation [27]. In a violent situation, an effective erection of the penis can be induced. The effective standard is that the penis maintains sufficient stiffness and can complete sexual intercourse [32]. PDE5 degraded cGMP, causing contraction of penile smooth muscle to make it fatigued. PDE5 inhibitors degraded cGMP by inhibiting PDE5 for the second messenger to longer lasting in the penile artery and smooth muscle cells and maintaining a long erection of the penis. Currently, the pharmacological mechanisms of PDE5 inhibitors, including sildenafil, tadalafil, and vardenafil, are similar after oral administration [27-31]. Stimulating state can induce an effective erection.

Methods of taking PDE5 inhibitors include on-demand treatment and regular treatment. It can be used as needed and taken about 1 hour before sexual contact [29]. The recommended dose of sildenafil for on-demand treatment is 50 mg and 100 mg, respectively [31, 32]. The effective rate of treatment for the general ED population was 77% and 84%, respectively [30-32]. The recommended dose of tadalafil on-demand treatment is l0 mg and 20 mg [28-31], and the treatment efficiency of the ED population was 67% and 8l%, respectively. The recommended dose for non-treatment is 10 mg and 20 mg, which is for the general ED population and the treatment efficiency is 76% and 80%, respectively [33, 34]. Regular treatment is another alternative way. Small sample clinical studies showed daily continuous service using sildenafil 50 mg for 4 weeks could improve cavernous artery blood flow and blood endothelial function, and vascular endothelial function was still improved after stopping the drugs [35-37]. ED patients with cardiovascular risk found that taking tadalafil 20 mg every other day would significantly improve vascular endothelial function after 4 weeks, and the effect could continue 2 weeks after withdrawal [34].

So far, there has been no multi-center double-blind or triple-blind research on the efficacy of the above three PDE5 inhibitors. Some patients, especially those with diabetes mellitus complicated with ED or radical prostatectomy, had a poor response to these drugs. Severe endothelial dysfunction and cavernous nerve injury are the main causes. Because the action of PDE5 inhibitors was dependent on endogenous NO formation, if endogenous bioavailable NO is insufficient due

to severe endothelial dysfunction or nerve damage, PDE5 inhibitors may not be sufficient to raise the level of cGMP above the necessary threshold. In addition, PDE5 inhibitors cannot reverse the potential vascular or neurological dysfunction associated with ED. Due to the risk of systemic vasodilation and severe hypotension, PDE5 inhibitors were forbidden to be combined with nitrate. Nevertheless, Kloner RA [38] suggested that after careful assessment, patients with ED could take nitrates at the right amount 24 hours after the last dose of short-acting PDE5i while 48 hours at least after the last dose of long-acting PDE5i so as to avoid accidents.

4.1.2. Supplementary Androgen Therapy

Functional changes and declines are normal outcomes in the aging process, and it is suitable for the endocrine system, especially the level of testosterone produced by the testes. A decrease in testosterone is accompanied by penile ED and a reduction in the supply of penile blood flow. In addition, increased cardiovascular risk and muscle atrophy decrease bone density and libido, all of these interact with testosterone metabolism [37, 39]. Androgen plays an important role in maintaining erectile function through four major mechanisms: impaired NO synthase release, altered PDE5 expression and activity, impaired cavernous nerve function, and penile vein occlusive disease. Androgen significantly affects the function of smooth muscle tissue in the corpus cavernosum. Studies have shown a close relationship between testosterone and ED and suggest that testosterone therapy may be a valuable option for a growing number of affected men [16, 27, 29].

For patients with not only ED but also low testosterone levels, supplementary androgen therapy, also known as testosterone replacement therapy, can improve erectile function in patients who do not respond to PDE5 inhibitors and may have synergistic effects with PDE5 inhibitors [39-41]. The oral androgen currently used for ED treatment was mainly testosterone undecanoate capsules. Androgen supplement was safe for patients with ED at low testosterone levels, but for patients with prostate cancer, supplementation with androgens may stimulate cancer progression and can be considered a contraindication [42].

4.1.3. Apomorphine

Apomorphine, acting on the central nervous system, was once used as a first-line drug for the treatment of ED. Japan's Takeda Co. Ltd. developed and released apomorphine sublingual tablets; it was approved for marketing in Europe and had proven effective in clinical trials in the United States, Europe, Canada and Australia [43-46]. It was mainly used for the treatment of patients with mild and moderate ED who had a partial erectile function. It is safe to start with 2 mg and increase the dose to 3 mg after at least 2 times [47]. It was a trial for many researchers trying to develop new drugs that target different central and peripheral molecular pathways. Sublingual apomorphine has a wide range of clinical and practical value because of its safety, convenience, tolerance and curative effect, but it also has side effects such as headache, dizziness, and lethargy, therefore it is not currently used as the first-line treatment for ED (Fig. **1** and Table **1**).

4.2. Combination Medications

In the treatment of ED, when a single drug is ineffective, a combination may have a synergistic effect, which can reduce the dose of the single drug with fewer adverse effects. There were varieties of clinical combinations available for clinical trials, but the study for combination therapy with sildenafil was a primary one [41, 42]. Some results showed that sildenafil combined with anti-oxidant drugs can improve the success rate of arterial ED treatment, neutralize oxidative stress products, and improve NO utilization. The combination of three drugs that improve endothelial function with vardenafil improves endothelial function in patients and is more beneficial to improving erectile function than vardenafil alone, but the sample size of this study is small. Thus, further research is still needed.

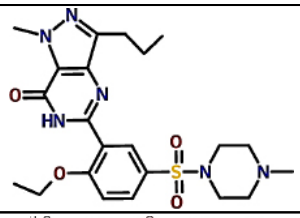
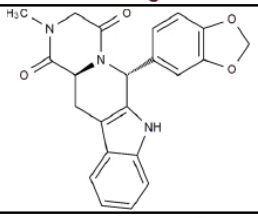
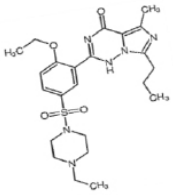
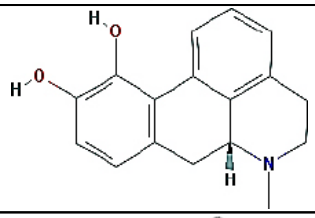
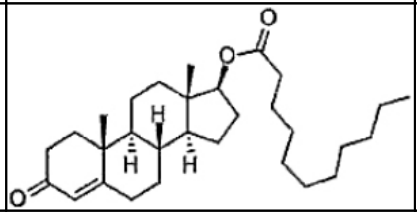
4.2.1. Alprostadil and Sildenafil

Bassil *et al.* [47] reported that oral sildenafil ineffective patients could be treated with prostaglandin mucosal administration of alprostadil. The study showed that 28 patients with ED who were included in the study achieved satisfactory results and did not have orthostatic hypotension or penile abnormalities. Nevertheless, the oral dose of sildenafil should be reduced to 50 mg when patients meet complications such as cardiovascular disorder, and it would be safe and effective. This combination regimen was especially suitable for those who feared injection into the cavernous body. In 2000, Mydlo *et al.* [48] reached similar conclusions: oral sildenafil combined with intraurethral alprostadil could achieve better efficacy than monotherapy for patients with ED.

4.2.2. Alpha Receptor Blocker and Sildenafil

In patients with psychological ED, combined with sildenafil and the receptor blocker doxazosin treatment, the effective rate can reach 79%, and no significant blood pressure fluctuations, while sildenafil and

Table 1. History and progression of conventional drugs for erectile dysfunction pharmacotherapy.

Drug		Chemical Structure	First Service Time	Current Situation
PDE5i	Sildenafil		1998	First-line drug
	Tadanafil		2003	First-line drug
	Vardenafil		2003	First-line drug
Apomorphine			2000	Non-first-line drug
Supplementary androgen therapy	Testosterone undecanoate		2009	Second-line drug

placebo combined with the control group, the efficiency was only 7%. Lin *et al.* [49] used a selective alpha receptor blocker, alfuzosin and sildenafil, in combination with ED in patients with lower urinary tract syndrome (LUTS). Compared with sildenafil alone, patients in the combination treatment group had significant improvement in nocturia, residual urine, maximum urinary flow rate and an international erectile function index. It also indicated that the program could achieve two-fold therapeutic effects for patients with ED who have LUTS.

4.2.3. Pentoxifylline and Sildenafil

Methylxanthine derivative pentoxifylline, which increases the deformability of red blood cells and inhibits platelet antibodies to improve capillary blood flow, is commonly used in the treatment of chronic occlusive arterial disease, and it can also improve penis blood flow and erectile function. Both *et al.* [50] performed a combination of sildenafil and pentoxifylline in the treatment of ED for 68 patients. In this study, patients were given sildenafil 1 hour before sexual intercourse, taking it 2 times a week, with a minimum dose of 50 mg for 4 weeks. After 4 weeks, the treatment was recommended to take pentoxifylline 3 times a day and the total dose was 1.2 g for 4 weeks. The efficacy was evaluated by the International Index of Erectile Function score. The results showed that the score of the combination group was significantly higher than that of the sildenafil group alone ($p < 0.001$). It has also been reported that pentoxifylline alone was not effective in patients with angiogenic impotence.

4.2.4. Losartan and Sildenafil

Long-term hypertension can lead to vascular tree structures, including cavernous blood vessels. Hypertension was considered to be one of the causes of organic ED by altering and inducing damage to the cavernous tissue. The angiotensin II receptor blocker losartan had a hypotensive effect. Cowart *et al.* [51] combined sildenafil with losartan in rats with hypertension and observed the effect of the regimen on the morphology and function of erectile tissue in rats. When compared to the single agent group, they discovered that the rats in the combination group showed improved penile erection. The content of alpha smooth muscle myofibrillin in cavernosal smooth muscle, cavernous artery smooth muscle and type III collagen was significantly lower than that in the control group, and the expression of endothelial nitric oxide syntheses was increased. These results suggested that a long-term combination of these two drugs could improve the morphology and function of erectile tissue. This finding provided a new treatment strategy for patients with impotence due to hypertension.

4.2.5. Quinapril and Sildenafil

A large number of animal and clinical studies have confirmed that angiotensin-converting enzyme inhibitor is safe and effective in the treatment of patients with hypertension and congestive heart failure. Lin *et al.* [49] reported that quinapril and sildenafil were used in patients with ED, and the efficacy was evaluated by international erectile function index, penile Doppler flow, blood pressure, blood lipids, and C-reactive protein. The results showed that compared with the placebo group, the combination of quinapril and sildenafil could significantly improve erectile function, and there was no significant difference in peripheral and penile vascular parameters. It demonstrated that this combination therapy was safe and effective.

4.3. Invasive Therapy

4.3.1. Intracavernosal Injection (ICI) Therapy

Intracavernous Injection (ICI) was an available method by injecting medicine directly into the corpus cavernosum to obtain an erection. The convenience of the injection system directly affected the patient's and his partner's satisfaction and compliance with the drug. Currently, a variety of injection systems are available. In the United States [6, 18, 41, 47], the most commonly used ICI medications were alprostadil and Trimix (a combination of papaverine, phentolamine and alprostadil).

4.3.2. Papaverine

Papaverine is a non-specific PDE inhibitor that can increase cAMP and cGMP concentrations in penile erectile tissue. The clinical dose of papaverine is usually 15-60 mg, making an effective effort for mental and neurological ED up to 80%, but relatively weak (36% to 50%) for blood vessels ED [52]. The advantages are low cost and stable at room temperature, while the main adverse reactions are sustained erection and fibrosis (incidence rates of 35% and 33%, respectively) and occasionally elevated serum transaminase.

4.3.3. Phentolamine

It is well known that phentolamine is a competitive antagonist of an anti-adrenergic receptor agent [41]; when applied alone, the penis can be erectile but not stiff, and it can be combined with papaverine. The power was obviously increased. Usually, 30 mg of papaverine is combined with 0.5 ~ 1 mg phentolamin.

4.3.4. Alprostadil

Currently, Alprostadil has three preparations for cavernous injection. Pediatric dosage form Prostin VR and injection freeze-dried powder Cavedect are both Pharmacia & Upjohn's products, and a compound composed of a-cyclodextrin, Edex is Schwarz Pharma's product. Alprostadil is the only sclerotherapy injection approved by the US FDA. The usual dose was 5 μg to 20 μg. Its efficacy is stronger than that of papaverine and a combination of papaverine and phentolamine. After regular treatment, the successful erection rate was over 70%. The incidence of ischemia (0.35% to 4%) and fibrosis (1% to 23%) were low, and the main adverse effect was erectile pain (17% to 34%) [53].

4.4. Vasoactive Intestinal Polypeptide

Vasoactive Intestinal Polypeptide is a kind of strong, smooth muscle relaxant, which can cause an erection but not stiffening when used alone, it had a success rate of 67% to 70% when combined with phentolamine [47, 50, 51]. The main adverse reactions to the drug were transient blush (53%), contusion (20%), pain at the injection site (11%), and skin flushing (9%). In Europe, compound preparations had been marketed but not yet been approved by the US FDA.

The main adverse events of ICI are persistent ED and fibrosis, which can be avoided by careful dose adjustment. Patients with sickle cell anemia, schizophrenia, and other serious mental illnesses or severe venous leaks should not be treated with ICI.

Table 2. Herbal medicine and their pharmacological effects for treatment of erectile dysfunction.

Herbal Medicine	Pharmacological Effects	Related Studies
Lepidium meyenii	Modulating the hypothalamus-pituitary axis Enhancing libido and fertility Regulating interaction between the glucosinolates and androgen receptor Promoting hormone secretion Improving sperm count and sperm motility Protecting sperm vitality against some toxic agents	Bogani P, 2006 [57] Rubio J, 2006 [58] Gasco M, 2007 [59]
Epimedium herbs	Inhibiting phosphodiesterase-5 Enhancing cGMP levels in corpus cavernosum muscles Elevating intracavernosal pressure Upregulating protein level of neuronal nitric oxide synthase	Xin ZC, 2003 [60] Liu WJ, 2005 [61]
Panax ginseng	Activating nitric oxide synthase (NOs) from endothelial cells and perivascular nerves Promoting to release NO	Kim HJ, 1998 [62] Zhang H, 2006 [63]
Tribulus terrestris	Increasing androgen secretion Elevating intracavernosal pressure	Gauthaman K, 2002 [64]
Yohimbine	Inhibiting sympathetic nerves Enhancing sexual arousal Accelerating the relase of NO from penile nerves	Simonsen U, 1997 [65]
Eurycoma longifolia	Enhancing testosterone and cGMP synthesis Improving sperm count and sperm motility	Chye PH, 2006 [66] Sambandan TG, 2006 [67]
Butea superba	Elevating intracavernosal pressure Relaxing corpus cavernosum smooth muscle	Tocharus C, 2006 [68]
Securidaca longipedunculata	Relaxing corpus cavernosum smooth muscle	Rakuambo NC, 2006 [69]

4.5. Prostaglandin E_1 Insertions

Prostaglandin E_1 is inserted into the urethra with a semi-solid ball to treat ED, while a band was placed at the base of the penis to increase the hardness of the erection. The clinical efficacy is lower than the intracavernosal injection of the penis [53, 54], and approximately 70% of patients were satisfied with this treatment. Adverse reactions included local pain (29% to 41%), dizziness (1.9% to 14%), and urethral bleeding (5%).

4.6. Penile Prosthetic Implants

Penile prosthetic implants were used extensively before oral drug promotion [2], and it had been listed as a non-recommended method in the treatment guidelines.

4.7. Potential Drugs and New Routes

Up to now, researchers from all over the world are still developing various drugs for the treatment of ED, such as PDE5i derivatives [18, 27], dopamine receptor agonists [55] (ABT-724 and ABT-670); melanin receptor agonist [55] (Melanotan acetate II); soluble guanylate cyclase agonist [18], heme-dependent activator (BAY63-2521 and BAY60-4552) and heme-independent activators (BAY 58-2667); Rho kinase inhibitors [54] (fasudil, Y-27632, SAR 407899), though these drugs are still on the *in vitro* or preclinical usage stage.

Various preclinical studies [53-56] based on protein therapy and gene therapy have shown that they are hopeful of restoring erectile function by regenerating cavernous vascular endothelial cells and cavernous nerves and inhibiting cavernous fibrosis. However, it has not yet entered the clinical trial stage due to the complexity of protein engineering and genetic engineering. ED has a variety of pathogenic mechanisms, and the combination of multiple drug treatment strategies may yield better results. Current preclinical data also lays a solid foundation for more effective drug therapy in the future.

4.8. Adjuvant Therapy

In addition, adjuvant therapy can often be used to improve the vascular endothelial function and increase the local circulating blood flow, including the combination of psychotropic drugs, *in vitro* low-energy shock wave therapy [28] and so on; on the other hand, they have not yet been certified or approved by the global guidelines.

4.9. Herbal and Traditional Medicine

Herbal medicines were recorded in many representative traditional Chinese masterpieces, such as *Bencao Gangmu.* Patients appear to benefit from herbal medicines because they come from natural plants, especially in Asian and African areas. These herbal therapies are selected to fight against dozens of diseases to stay fit. In this review, we gave a perspective of medicinal plants studied in ED therapy (Table **2**) [57-69], and fully understanding the pharmacological effects of these potential phytotherapies is necessary for urologists. Although herbal medicines might play functional roles in the treatment of ED, they are still difficult to be used for conventional therapy. First of all, current research is mainly based on animal experiments, but physical qualities, as well as tolerance to herbal therapy of patients, vary from Eastern to Western countries; there are few possibilities to carry out universal studies worldwide. Secondly, despite a large market demand, herbal medications extracted from diverse batches of plants are hard to make quality control for different growing conditions, extraction techniques and storage standardizations. Thirdly, there is insufficient financial support for herbal research, so we cannot identify the active ingredients in the drugs for ED therapy quickly and accurately. Therefore, we should respect the wishes of each patient with ED and make individualized treatment strategies to ensure a satisfactory outcome.

CONCLUSION

Because of the immediate efficacy of PDE5 inhibitors in the pharmacotherapy of ED, they are often used as the first-line drugs clinically. However, people have made a deeper understanding of the physiological mechanism of penile erection, which has led to the breakthrough of new drugs, especially for patients with ED who are not sensitive to PDE5 inhibitors. *In vitro* low-energy, shock wave and stem cell transplantations are representatives and innovative creations, and we believe that they would be widely used to overcome refractory ED. In the future, precision and individual medical care will become the trend and the new guideline with new curable methods or drugs for treating ED will become a reality.

LIST OF ABBREVIATIONS

CNS = Central Nervous System

DA = Dopamine

PNS = Peripheral Nervous System

Ach = Acetylcholine

VEC = Vascular Endothelial Cell

EDRF = Endothelium Derived Relaxing Factor

NO = Nitric Oxide

SMC = Smooth Muscle Cell

SM = Smooth Muscle

GCs = Guanylate Cyclase

GTP = Guanosine Triphosphate

cGMP = Cyclic Guanosine Monophosphate

PDE5i = Phosphodiesterase-5 Inhibitors

AT = Androgen Therapy

Apo = Apomorphine

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Shamloul, R.; Ghanem, H. Erectile dysfunction. *Lancet,* **2013**, *381*(9861), 153-165. http://dx.doi.org/10.1016/S0140-6736(12)60520-0 PMID: 23040455

[2] Li, T.; Wu, C.; Fu, F.; Qin, F.; Wei, Q.; Yuan, J. Association between use of aspirin or non-aspirin non-steroidal anti-inflammatory drugs and erectile dysfunction: A systematic review. *Medicine (Baltimore),* **2018**, *97*(28), e11367. http://dx.doi.org/10.1097/MD.0000000000011367 PMID: 29995772

[3] Prakash, O.; Rao, T.S. Sexuality research in India: An update. *Indian J. Psychiatry,* **2010**, *52*(7), S260-S263. http://dx.doi.org/10.4103/0019-5545.69243 PMID: 21836690

[4] Zhang, K.; Yu, W.; He, Z.J.; Jin, J. Help-seeking behavior for erectile dysfunction: A clinic-based survey in China. *Asian J. Androl.,* **2014**, *16*(1), 131-135. http://dx.doi.org/10.4103/1008-682X.122350 PMID: 24369146

[5] El-Sakka, A.I. Pharmacotherapy for erectile dysfunction in

diabetic males. *Expert Opin. Pharmacother.,* **2018**, *19*(12), 1345-1356.
http://dx.doi.org/10.1080/14656566.2018.1505866 PMID: 30106605

[6] Feldman, H.A.; Goldstein, I.; Hatzichristou, D.G.; Krane, R.J.; McKinlay, J.B. Impotence and its medical and psychosocial correlates: Results of the massachusetts male aging study. *J. Urol.,* **1994**, *151*(1), 54-61.
http://dx.doi.org/10.1016/S0022-5347(17)34871-1 PMID: 8254833

[7] Zhang, X.; Yang, B.; Li, N.; Li, H. Prevalence and risk factors for erectile dysfunction in Chinese adult males. *J. Sex. Med.,* **2017**, *14*(10), 1201-1208.
http://dx.doi.org/10.1016/j.jsxm.2017.08.009 PMID: 28874333

[8] Grossmann, M.; Matsumoto, A.M. A perspective on middle-aged and older men with functional hypogonadism: Focus on holistic management. *J. Clin. Endocrinol. Metab.,* **2017**, *102*(3), 1067-1075.
http://dx.doi.org/10.1210/jc.2016-3580 PMID: 28359097

[9] Klein, R.; Klein, B.E.; Lee, K.E.; Moss, S.E.; Cruickshanks, K.J. Prevalence of self-reported erectile dysfunction in people with long-term IDDM. *Diabetes Care,* **1996**, *19*(2), 135-141.
http://dx.doi.org/10.2337/diacare.19.2.135 PMID: 8718433

[10] Khoo, J.; Piantadosi, C.; Worthley, S.; Wittert, G.A. Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. *Int. J. Obes.,* **2010**, *34*(9), 1396-1403.
http://dx.doi.org/10.1038/ijo.2010.76 PMID: 20404829

[11] McWaine, D.E.; Procci, W.R. Drug-induced sexual dysfunction. *Med. Toxicol. Adverse Drug Exp.,* **1988**, *3*(4), 289-306.
PMID: 3054427

[12] Defade, B.P.; Carson, C.C., III; Kennelly, M.J. Postprostatectomy erectile dysfunction: The role of penile rehabilitation. *Rev. Urol.,* **2011**, *13*(1), 6-13.
PMID: 21826123

[13] Yassin, A.A.; Saad, F. Testosterone and erectile dysfunction. *J. Androl.,* **2008**, *29*(6), 593-604.
http://dx.doi.org/10.2164/jandrol.107.004630 PMID: 18641415

[14] Travison, T.G.; Shabsigh, R.; Araujo, A.B.; Kupelian, V.; O'Donnell, A.B.; McKinlay, J.B. The natural progression and remission of erectile dysfunction: Results from the massachusetts male aging study. *J. Urol.,* **2007**, *177*(1), 241-246.
http://dx.doi.org/10.1016/j.juro.2006.08.108 PMID: 17162054

[15] Kouidrat, Y.; Pizzol, D.; Cosco, T.; Thompson, T.; Carnaghi, M.; Bertoldo, A.; Solmi, M.; Stubbs, B.; Veronese, N. High prevalence of erectile dysfunction in diabetes: A systematic review and meta-analysis of 145 studies. *Diabet. Med.,* **2017**, *34*(9), 1185-1192.
http://dx.doi.org/10.1111/dme.13403 PMID: 28722225

[16] Hannan, J.L.; Blaser, M.C.; Oldfield, L.; Pang, J.J.; Adams, S.M.; Pang, S.C.; Adams, M.A. Morphological and functional evidence for the contribution of the pudendal artery in aging-induced erectile dysfunction. *J. Sex. Med.,* **2010**, *7*(10), 3373-3384.
http://dx.doi.org/10.1111/j.1743-6109.2010.01920.x PMID: 20584117

[17] Ferrini, M.G.; Kovanecz, I.; Sanchez, S.; Vernet, D.; Davila, H.H.; Rajfer, J.; Gonzalez-Cadavid, N.F. Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol. Reprod.,* **2007**, *76*(5), 915-923.
http://dx.doi.org/10.1095/biolreprod.106.059642 PMID: 17287493

[18] Gruenwald, I.; Appel, B.; Vardi, Y. Low-intensity extracorporeal shock wave therapy-a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. *J. Sex. Med.,* **2012**, *9*(1), 259-264.
http://dx.doi.org/10.1111/j.1743-6109.2011.02498.x PMID: 22008059

[19] Feng, Y.; LoGrasso, P.V.; Defert, O.; Li, R. Rho Kinase (ROCK) inhibitors and their therapeutic potential. *J. Med. Chem.,* **2016**, *59*(6), 2269-2300.
http://dx.doi.org/10.1021/acs.jmedchem.5b00683 PMID: 26486225

[20] El-Sakka, A.I.; Lue, T.F. Physiology of penile erection. *Sci. World J.,* **2004**, *4*(Suppl. 1), 128-134.
http://dx.doi.org/10.1100/tsw.2004.58 PMID: 15349538

[21] Yavuzgil, O.; Altay, B.; Zoghi, M.; Gürgün, C.; Kayikçioğlu, M.; Kültürsay, H. Endothelial function in patients with vasculogenic erectile dysfunction. *Int. J. Cardiol.,* **2005**, *103*(1), 19-26.
http://dx.doi.org/10.1016/j.ijcard.2004.07.004 PMID: 16061118

[22] Foresta, C.; Caretta, N.; Lana, A.; Cabrelle, A.; Palù, G.; Ferlin, A. Circulating endothelial progenitor cells in subjects with erectile dysfunction. *Int. J. Impot. Res.,* **2005**, *17*(3), 288-290.
http://dx.doi.org/10.1038/sj.ijir.3901311 PMID: 15729373

[23] Dean, R.C.; Lue, T.F. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol. Clin. North Am.,* **2005**, *32*(4), 379-395.
http://dx.doi.org/10.1016/j.ucl.2005.08.007 PMID: 16291031

[24] Peak, T.C.; Yafi, F.A.; Sangkum, P.; Hellstrom, W.J. Emerging drugs for the treatment of erectile dysfunction. *Expert Opin. Emerg. Drugs,* **2015**, *20*(2), 263-275.
http://dx.doi.org/10.1517/14728214.2015.1021682 PMID: 25740087

[25] Gur, S.; Kadowitz, P.J.; Hellstrom, W.J. Exploring the potential of NO-independent stimulators and activators of soluble guanylate cyclase for the medical treatment of erectile dysfunction. *Curr. Pharm. Des.,* **2010**, *16*(14), 1619-1633.
http://dx.doi.org/10.2174/138161210791164162 PMID: 20201788

[26] Sopko, N.A.; Hannan, J.L.; Bivalacqua, T.J. Understanding and targeting the Rho kinase pathway in erectile dysfunction. *Nat. Rev. Urol.,* **2014**, *11*(11), 622-628.
http://dx.doi.org/10.1038/nrurol.2014.278 PMID: 25311680

[27] Guagnini, F.; Ferazzini, M.; Grasso, M.; Blanco, S.; Croci, T. Erectile properties of the Rho-kinase inhibitor SAR407899 in diabetic animals and human isolated *Corpora cavernosa*. *J. Transl. Med.,* **2012**, *10*(1), 59.
http://dx.doi.org/10.1186/1479-5876-10-59 PMID: 22444253

[28] Usta, M.F.; Sanabria, J.; Bivalacqua, T.J.; Hellstrom, W.J. Feline penile erection induced by topical glans penis application of combination alprostadil and SEPA (Topiglan). *Int. J. Impot. Res.,* **2004**, *16*(1), 73-77.
http://dx.doi.org/10.1038/sj.ijir.3901145 PMID: 14963475

[29] Meadows, K.L.; Rushing, C.; Honeycutt, W.; Latta, K.; Howard, L.; Arrowood, C.A.; Niedzwiecki, D.; Hurwitz, H.I. Treatment of palmar-plantar erythrodysesthesia (PPE)

with topical sildenafil: A pilot study. *Support. Care Cancer,* **2015**, *23*(5), 1311-1319. http://dx.doi.org/10.1007/s00520-014-2465-z PMID: 25341548

[30] Keating, G.M.; Scott, L.J. Vardenafil: A review of its use in erectile dysfunction. *Drugs,* **2003**, *63*(23), 2673-2703. http://dx.doi.org/10.2165/00003495-200363230-00010 PMID: 14636086

[31] Mathers, M.J.; Klotz, T.; Brandt, A.S.; Roth, S.; Sommer, F. Long-term treatment of erectile dysfunction with a phosphodiesterase-5 inhibitor and dose optimization based on nocturnal penile tumescence. *BJU Int.,* **2008**, *101*(9), 1129-1134. http://dx.doi.org/10.1111/j.1464-410X.2007.07376.x PMID: 18190629

[32] Vardi, Y.; Appel, B.; Ofer, Y.; Greunwald, I.; Dayan, L.; Jacob, G. Effect of chronic sildenafil treatment on penile endothelial function: A randomized, double-blind, placebo controlled study. *J. Urol.,* **2009**, *182*(6), 2850-2855. http://dx.doi.org/10.1016/j.juro.2009.08.025 PMID: 19837434

[33] Rosano, G.M.; Aversa, A.; Vitale, C.; Fabbri, A.; Fini, M.; Spera, G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur. Urol.,* **2005**, *47*(2), 214-220. http://dx.doi.org/10.1016/j.eururo.2004.10.002 PMID: 15661417

[34] Santi, D.; Granata, A.R.; Guidi, A.; Pignatti, E.; Trenti, T.; Roli, L.; Bozic, R.; Zaza, S.; Pacchioni, C.; Romano, S.; Nofer, J.R.; Rochira, V.; Carani, C.; Simoni, M. Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: A randomized, double-blind, prospective trial. *Eur. J. Endocrinol.,* **2016**, *174*(4), 513-522. http://dx.doi.org/10.1530/EJE-15-1100 PMID: 26792933

[35] Musicki, B.; Burnett, A.L. Endothelial dysfunction in diabetic erectile dysfunction. *Int. J. Impot. Res.,* **2007**, *19*(2), 129-138. http://dx.doi.org/10.1038/sj.ijir.3901494 PMID: 16775612

[36] Angulo, J.; González-Corrochano, R.; Cuevas, P.; Fernández, A.; La Fuente, J.M.; Rolo, F.; Allona, A.; Sáenz de Tejada, I. Diabetes exacerbates the functional deficiency of NO/cGMP pathway associated with erectile dysfunction in human corpus cavernosum and penile arteries. *J. Sex. Med.,* **2010**, *7*(2 Pt 1), 758-768. http://dx.doi.org/10.1111/j.1743-6109.2009.01587.x PMID: 19912487

[37] Webb, D.J.; Muirhead, G.J.; Wulff, M.; Sutton, J.A.; Levi, R.; Dinsmore, W.W. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J. Am. Coll. Cardiol.,* **2000**, *36*(1), 25-31. http://dx.doi.org/10.1016/S0735-1097(00)00705-1 PMID: 10898408

[38] Kloner, R.A.; Goggin, P.; Goldstein, I.; Hackett, G.; Kirby, M.G.; Osterloh, I.; Parker, J.D.; Sadovsky, R. A new perspective on the nitrate-phosphodiesterase type 5 inhibitor interaction. *J. Cardiovasc. Pharmacol. Ther.,* **2018**, *23*(5), 375-386. http://dx.doi.org/10.1177/1074248418771896 PMID: 29739235

[39] Christou, M.A.; Christou, P.A.; Markozannes, G.; Tsatsoulis, A.; Mastorakos, G.; Tigas, S. Effects of anabolic androgenic steroids on the reproductive system of athletes and recreational users: A systematic review and meta-analysis. *Sports Med.,* **2017**, *47*(9), 1869-1883. http://dx.doi.org/10.1007/s40279-017-0709-z PMID: 28258581

[40] Aversa, A.; Isidori, A.M.; De Martino, M.U.; Caprio, M.; Fabbrini, E.; Rocchietti-March, M.; Frajese, G.; Fabbri, A. Androgens and penile erection: Evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. *Clin. Endocrinol. (Oxf.),* **2000**, *53*(4), 517-522. http://dx.doi.org/10.1046/j.1365-2265.2000.01118.x PMID: 11012578

[41] Wessells, H.; Levine, N.; Hadley, M.E.; Dorr, R.; Hruby, V. Melanocortin receptor agonists, penile erection, and sexual motivation: Human studies with Melanotan II. *Int. J. Impot. Res.,* **2000**, *12*(S4), S74-S79. http://dx.doi.org/10.1038/sj.ijir.3900582 PMID: 11035391

[42] Anitha, B.; Inamadar, A.C.; Ragunatha, S. Finasteride-its impact on sexual function and prostate cancer. *J. Cutan. Aesthet. Surg.,* **2009**, *2*(1), 12-16. http://dx.doi.org/10.4103/0974-2077.53093 PMID: 20300365

[43] Heaton, J.P. Apomorphine: An update of clinical trial results. *Int. J. Impot. Res.,* **2000**, *12*(S4), S67-S73. http://dx.doi.org/10.1038/sj.ijir.3900581 PMID: 11035390

[44] Dula, E.; Keating, W.; Siami, P.F.; Edmonds, A.; O'neil, J.; Buttler, S. Efficacy and safety of fixed-dose and dose-optimization regimens of sublingual apomorphine *versus* placebo in men with erectile dysfunction. *Urology,* **2000**, *56*(1), 130-135. http://dx.doi.org/10.1016/S0090-4295(00)00575-6 PMID: 10869641

[45] Heaton, J.P. Characterising the benefit of apomorphine SL (Uprima) as an optimised treatment for representative populations with erectile dysfunction. *Int. J. Impot. Res.,* **2001**, *13*(S3), S35-S39. http://dx.doi.org/10.1038/sj.ijir.3900721 PMID: 11477490

[46] Dula, E.; Bukofzer, S.; Perdok, R.; George, M. Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. *Eur. Urol.,* **2001**, *39*(5), 558-3. http://dx.doi.org/10.1159/000052503 PMID: 11464037

[47] Patel, M.V.; Kolasa, T.; Mortell, K.; Matulenko, M.A.; Hakeem, A.A.; Rohde, J.J.; Nelson, S.L.; Cowart, M.D.; Nakane, M.; Miller, L.N.; Uchic, M.E.; Terranova, M.A.; El-Kouhen, O.F.; Donnelly-Roberts, D.L.; Namovic, M.T.; Hollingsworth, P.R.; Chang, R.; Martino, B.R.; Wetter, J.M.; Marsh, K.C.; Martin, R.; Darbyshire, J.F.; Gintant, G.; Hsieh, G.C.; Moreland, R.B.; Sullivan, J.P.; Brioni, J.D.; Stewart, A.O. Discovery of 3-methyl-N-(1-oxy-3′,4′,5′,6′-tetrahydro-2'H-[2,4'-bipyridine]-1′-ylmethyl)benzamide (ABT-670), an orally bioavailable dopamine D4 agonist for the treatment of erectile dysfunction. *J. Med. Chem.,* **2006**, *49*(25), 7450-7465. http://dx.doi.org/10.1021/jm060662k PMID: 17149874

[48] Mydlo, J.H.; Volpe, M.A.; Macchia, R.J. Initial results utilizing combination therapy for patients with a suboptimal response to either alprostadil or sildenafil monotherapy. *Eur. Urol.,* **2000**, *38*(1), 30-34. http://dx.doi.org/10.1159/000020248 PMID: 10859438

[49] Lin, C.S.; Xin, Z.C.; Wang, Z.; Deng, C.; Huang, Y.C.; Lin, G.; Lue, T.F. Stem cell therapy for erectile dysfunction: A critical review. *Stem Cells Dev.,* **2012**, *21*(3), 343-351. http://dx.doi.org/10.1089/scd.2011.0303 PMID: 21793654

[50] Both, S. Recent developments in psychopharmaceutical approaches to treating female sexual interest and arousal disorder. *Curr. Sex. Health Rep.,* **2017**, *9*(4), 192-199. http://dx.doi.org/10.1007/s11930-017-0124-3 PMID: 29225554

[51] Cowart, M.; Latshaw, S.P.; Bhatia, P.; Daanen, J.F.; Rohde, J.; Nelson, S.L.; Patel, M.; Kolasa, T.; Nakane, M.; Uchic, M.E.; Miller, L.N.; Terranova, M.A.; Chang, R.; Donnelly-Roberts, D.L.; Namovic, M.T.; Hollingsworth, P.R.; Martino, B.R.; Lynch, J.J., III; Sullivan, J.P.; Hsieh, G.C.; Moreland, R.B.; Brioni, J.D.; Stewart, A.O. Discovery of 2-(4-pyridin-2-ylpiperazin-1-ylmethyl)-1H-benzimidazole (ABT-724), a dopaminergic agent with a novel mode of action for the potential treatment of erectile dysfunction. *J. Med. Chem.,* **2004**, *47*(15), 3853-3864. http://dx.doi.org/10.1021/jm030505a PMID: 15239663

[52] Liu, J.; Zhou, F.; Li, G.Y.; Wang, L.; Li, H.X.; Bai, G.Y.; Guan, R.L.; Xu, Y.D.; Gao, Z.Z.; Tian, W.J.; Xin, Z.C. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. *Int. J. Mol. Sci.,* **2013**, *14*(5), 10661-10673. http://dx.doi.org/10.3390/ijms140510661 PMID: 23698784

[53] Melman, A.; Bar-Chama, N.; McCullough, A.; Davies, K.; Christ, G. hMaxi-K gene transfer in males with erectile dysfunction: Results of the first human trial. *Hum. Gene Ther.,* **2006**, *17*(12), 1165-1176. http://dx.doi.org/10.1089/hum.2006.17.1165 PMID: 17134370

[54] Bahk, J.Y.; Jung, J.H.; Han, H.; Min, S.K.; Lee, Y.S. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: Preliminary report of 7 cases. *Exp. Clin. Transplant.,* **2010**, *8*(2), 150-160. PMID: 20565373

[55] Kitrey, N.D.; Gruenwald, I.; Appel, B.; Shechter, A.; Massarwa, O.; Vardi, Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: A double-blind, sham controlled study. *J. Urol.,* **2016**, *195*(5), 1550-1555. http://dx.doi.org/10.1016/j.juro.2015.12.049 PMID: 26694904

[56] Ciccone, M.M.; Notarnicola, A.; Scicchitano, P.; Sassara, M.; Carbonara, S.; Maiorano, M.; Moretti, B. Shockwave therapy in patients with peripheral artery disease. *Adv. Ther.,* **2012**, *29*(8), 698-707. http://dx.doi.org/10.1007/s12325-012-0038-4 PMID: 22869515

[57] Bogani, P.; Simonini, F.; Iriti, M.; Rossoni, M.; Faoro, F.; Poletti, A.; Visioli, F. *Lepidium meyenii* (Maca) does not exert direct androgenic activities. *J. Ethnopharmacol.,* **2006**, *104*(3), 415-417. http://dx.doi.org/10.1016/j.jep.2005.09.028 PMID: 16239088

[58] Rubio, J.; Riqueros, M.I.; Gasco, M.; Yucra, S.; Miranda, S.; Gonzales, G.F. *Lepidium meyenii* (Maca) reversed the lead acetate induced - damage on reproductive function in male rats. *Food Chem. Toxicol.,* **2006**, *44*(7), 1114-1122. http://dx.doi.org/10.1016/j.fct.2006.01.007 PMID: 16510228

[59] Gasco, M.; Aguilar, J.; Gonzales, G.F. Effect of chronic treatment with three varieties of *Lepidium meyenii* (Maca) on reproductive parameters and DNA quantification in adult male rats. *Andrologia,* **2007**, *39*(4), 151-158. http://dx.doi.org/10.1111/j.1439-0272.2007.00783.x PMID: 17683465

[60] Xin, Z.C.; Kim, E.K.; Lin, C.S.; Liu, W.J.; Tian, L.; Yuan, Y.M.; Fu, J. Effects of icariin on cGMP-specific PDE5 and cAMP-specific PDE4 activities. *Asian J. Androl.,* **2003**, *5*(1), 15-18. PMID: 12646997

[61] Liu, W.J.; Xin, Z.C.; Xin, H.; Yuan, Y.M.; Tian, L.; Guo, Y.L. Effects of icariin on erectile function and expression of nitric oxide synthase isoforms in castrated rats. *Asian J. Androl.,* **2005**, *7*(4), 381-388. http://dx.doi.org/10.1111/j.1745-7262.2005.00066.x PMID: 16281085

[62] Kim, H.J.; Woo, D.S.; Lee, G.; Kim, J.J. The relaxation effects of ginseng saponin in rabbit corporal smooth muscle: Is it a nitric oxide donor? *Br. J. Urol.,* **1998**, *82*(5), 744-748. http://dx.doi.org/10.1046/j.1464-410X.1998.00811.x PMID: 9839593

[63] Zhang, H.; Zhou, Q.M.; Li, X.D.; Xie, Y.; Duan, X.; Min, F.L.; Liu, B.; Yuan, Z.G. Ginsenoside R(e) increases fertile and asthenozoospermic infertile human sperm motility by induction of nitric oxide synthase. *Arch. Pharm. Res.,* **2006**, *29*(2), 145-151. http://dx.doi.org/10.1007/BF02974276 PMID: 16526279

[64] Gauthaman, K.; Adaikan, P.G.; Prasad, R.N. Aphrodisiac properties of *Tribulus terrestris* extract (Protodioscin) in normal and castrated rats. *Life Sci.,* **2002**, *71*(12), 1385-1396. http://dx.doi.org/10.1016/S0024-3205(02)01858-1 PMID: 12127159

[65] Simonsen, U.; Prieto, D.; Hernández, M.; Sáenz de Tejada, I.; García-Sacristán, A. Prejunctional alpha 2-adrenoceptors inhibit nitrergic neurotransmission in horse penile resistance arteries. *J. Urol.,* **1997**, *157*(6), 2356-2360. http://dx.doi.org/10.1016/S0022-5347(01)64780-3 PMID: 9146670

[66] Chye, P.H. Traditional Asian folklore medicines in sexual health. *Indian J. Urol.,* **2006**, *22*(3), 241-245. http://dx.doi.org/10.4103/0970-1591.27632

[67] Sambandan, T.G.; Rha, C.; Kadir, A.A. Bioactive fraction of *Eurycoma longifolia*. Patent No.: US 7132117 B2, **2006**.

[68] Tocharus, C.; Smitasiri, Y.; Jeenapongsa, R. *Butea superba* Roxb. enhances penile erection in rats. *Phytother. Res.,* **2006**, *20*(6), 484-489. http://dx.doi.org/10.1002/ptr.1883 PMID: 16619349

[69] Rakuambo, N.C.; Meyer, J.J.; Hussein, A.; Huyser, C.; Mdlalose, S.P.; Raidani, T.G. *In vitro* effect of medicinal plants used to treat erectile dysfunction on smooth muscle relaxation and human sperm. *J. Ethnopharmacol.,* **2006**, *105*(1-2), 84-88. http://dx.doi.org/10.1016/j.jep.2005.10.008 PMID: 16309865