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REVIEW ARTICLE

A Holistic View on Erectile Dysfunction: South African Medicinal Plants as Sustainable Alternative Therapies

Siyabonga Samuel Rayise[1], Chinenyenwa Fortune Chukwuneme[2*], Samkeliso Takaidza[2] and Cornelius Ssemakalu[2]

[1]Department of Health Sciences, Faculty of Applied and Computer Sciences, Vaal University of Technology, Vanderbijlpark - 1911, Gauteng, South Africa
[2]Department of Natural Sciences, Faculty of Applied and Computer Sciences, Vaal University of Technology, Vanderbijlpark - 1911, Gauteng, South Africa; corneliuss@vut.ac.za

Abstract

Erectile dysfunction is a common problem affecting men worldwide, especially as they age. This condition is characterized by the inability to achieve or maintain an erection firm enough for sexual intercourse and may result from various factors, including vascular, neurogenic, hormonal, and psychological. Common first-line treatment options for the disease have relied on phosphodiesterase-5 inhibitors such as sildenafil (Viagra), which are costly, inaccessible, and sometimes result in adverse health effects. Consequently, there has been increasing interest in exploring medicinal plants as alternative remedies because of their easy access and affordability. In South Africa, 75 plant species with properties that affect testosterone levels, luteinizing hormone, and follicle-stimulating hormone are used as aphrodisiacs. Some plant extracts can increase blood testosterone concentrations and stimulate penile erection by maintaining nitric oxide levels. This paper presents current information about the possible utilization of South African medicinal plants as viable and readily available therapeutic alternatives for managing erectile dysfunction. In addition, it discusses in detail the various mechanisms of action of medicinal plants in managing the disease. The information on the efficacy of African medicinal plants in managing erectile dysfunction provided in this review will help increase awareness of the sustainable use of natural products. It may serve as a basis for including indigenous herbal remedies in the guidelines for erectile dysfunction management as potential treatment options in Africa.

Keywords: Aphrodisiacs, Herbal Medicine, Phosphodiesterase-5 Inhibitors, Plant Extracts, Testosterone

1. Introduction

Erectile dysfunction is the inability to achieve an erection strong enough to perform satisfactorily during sexual activity[1]. This global problem affects men of all ages but is more common in older men[2]. By 2025, the worldwide prevalence of ED is projected to reach 322 million[3]. The underlying causes of ED can be classified into non-endocrine and endocrine factors[4]. The most common form of non-endocrine ED is vasculogenic, which involves arterial inflow disruption and corporal veno-occlusion. Neurogenic ED affects innervation and nervous function, whereas endocrine ED is associated with reduced serum testosterone levels[5].

Certain oral medications, known as phosphodiesterase type 5 (PDE-5) inhibitors, are the most prescribed therapy for the disease. These medications prolong erection by preventing the PDE-5 enzyme from neutralizing cyclic GMP (cGMP)[6]. When sexual stimulation occurs, Nitric Oxide (NO) is released from non-adrenergic non-cholinergic (NANC) nerve fibres and endothelial cells due to increased testosterone

*Author for correspondence

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levels. Nitric oxide enters the corporal smooth muscle and acts as an activator for Guanylate Cyclase (GC), by catalyzing the conversion of Guanosine Triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Cyclic GMP, on the other hand, activates protein kinase G and prevents Ca^{2+} from entering the corporal smooth muscle[7,8]. The decline in cytosolic Ca^{2+} concentration causes the vascular and corporal smooth muscle cells to relax, resulting in vasodilation, increased flow of arterial blood towards the corpora caversona, and penile erection (Figure 1)[9].

Although PDE-5 inhibitors are effective, they are expensive, have side effects, and are not easily accessible in low-to middle-income countries[8]. As a result, medicinal plants have been explored as alternative options because of their affordability and availability[10]. This review examines the potential use of medicinal plants in Africa as safe and affordable remedies for ED and highlights their intricate roles in boosting testosterone levels in erectile dysfunction individuals. By identifying natural products that can compete against PDE-5 inhibitors, individuals with socioeconomic constraints will have better access to ED treatment.

2. Global Prevalence of Erectile Dysfunction

According to global estimates, the prevalence of erectile dysfunction ranges from 2% in men in their twenties to over 80% in men older than 75 years[3]. A Massachusetts Male Aging Study conducted in 1994 showed a high prevalence of ED and estimated that 150 million men have this condition[11]. It has also been predicted that by 2025, this number will rise to 322 million[3].

Several studies have been conducted globally in recent decades to establish the prevalence of ED, with some studies indicating that its prevalence rates are dependent on factors such as sample size, methodology used, target group, and the definition used[12,13]. In other studies, age has been identified as the leading risk factor for ED, with its rising prevalence associated with the global aging population[11,14,15]. Other risk factors independently linked to ED include Cardiovascular Diseases (CVD), diabetes, Benign Prostatic Hyperplasia (BPH), and depression[15,16].

Among countries, factors such as health, race and culture may determine the prevalence of ED[17]. For instance, people's perspectives about sex and the influence of ED on the quality of life can vary

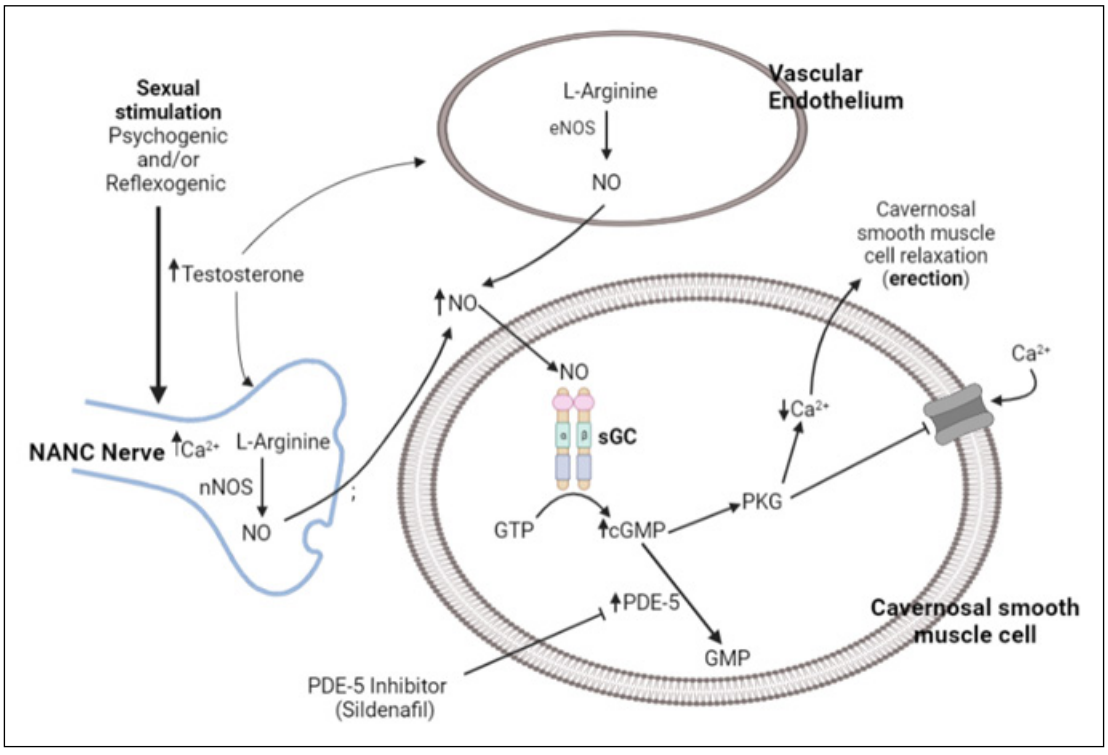


Figure 1. Mechanisms of improving cGMP levels by PDE-5 inhibitors to enhance penile erection.

considerably across cultures. Hence, it is important to study ED and the treatment options available to affected individuals across several countries, particularly across cultures other than those of industrialized countries, where nearly all studies covering this topic have been conducted to date.

3. Erectile Dysfunction in Africa

Many studies on erectile dysfunction have been carried out within the African continent. A study conducted in Morocco by Berrada *et al.,*[18] evaluated the incidence and risk factors associated with ED in a population-based sample of 655 men, whose age were above 25. The results demonstrated that the cohort's ED incidence, comorbidities, and risk factors were identical to those reported in Western countries. The overall prevalence of ED in the sample was 54%, with a significant increase in incidence with age. The risk factors for this group were heart disease, diabetes, smoking, and hypertension[18]. In addition, the estimated rates of men attending primary care clinics in Egypt, Pakistan, and Nigeria were reported to be 63.6%, 80.8%, and 57.4%, respectively[19,20].

Studies conducted in South Africa, such as those by De Klerk *et al.,*[21] and Lockhat *et al.,*[22], have indicated a high incidence of erectile dysfunction in men seeking medical care at primary care clinics. In a cross-sectional study conducted in KwaZulu-Natal, an overall prevalence of 64.9% was found in men above 18 years, with 14.6% reporting mild, 19.9% moderate, and 30.4% severe ED[22]. The study also found that ED increased with age and demonstrated a strong correlation with economic status and comorbidities. Similarly, a Western Cape study found that more than 70% of men attending primary care clinics experienced some degree of ED, with 45% experiencing moderate or complete ED[22]. These findings highlight the need for increased awareness of ED and improved access to treatment in South Africa.

4. Testosterone and Erectile Dysfunction

Testosterone is an androgen that stimulates the development of male characteristics and is produced by the Leydig cells in the testis[23]. Low serum testosterone levels have been linked to ED in aging males[24]. Recent studies have established an association between low serum testosterone levels and ED. Testosterone Replacement Therapy (TRT) has been successfully used with PDE-5 inhibitors in men with testosterone deficiency who were initially unresponsive to PDE-5 inhibitors[25]. Becker *et al.,*[26] showed that systemic testosterone levels increased in healthy subjects during penile erection and cavernous testosterone levels. However, this increase was less pronounced in subjects with erectile dysfunction[26]. According to the study, the mechanisms by which the erectile process is based are affected by testosterone[26]. In another study by Yassin *et al.*[27], the effects of reverting testosterone levels to normal were examined in men with ED and low sexual drive accompanied by other comorbidities. The authors reported that more than 50% of patients experienced an improvement in erectile function when intramuscular long-acting testosterone undecanoate (TRT) was administered. Furthermore, castration in animal models, which causes testosterone deficiency, leads to an impairment in the release of nitric oxide and a reduction in the levels and activity of PDE-5[28,29]. However, testosterone treatment has been shown to restore NO release and PDE-5 expression and activity. Testosterone exerts a dual effect on the nitric oxide-cGMP pathway, including stimulating both the erection initiator, NOS and its terminator PDE-5, thereby balancing the process[30]. This action of testosterone can be interpreted as a homeostatic mechanism that maintains a constant ratio of critical enzymes in this pathway.

5. Treatment of Erectile Dysfunction with Phosphodiesterase Type 5(PDE-5) Inhibitors

Phosphodiesterase type 5 (PDE-5) inhibitors are drugs that dilate the corpora cavernosa of the penis and facilitate erection by stimulating sexual desire[31]. These drugs act by selectively inhibiting the PDE-5 enzyme, increasing cGMP levels, and promoting smooth muscle relaxation for erection to occur (Figure 1)[30]. This specific function of PDE-5 inhibitors was discovered accidentally

during an investigation around hypertension and angina[32]. Presently, seven PDE-5 inhibitors are approved by the Food and Drug Administration (FDA), including sildenafil, tadalafil, vardenafil, avanafil, and mirodenafilandlodenafil[32]. Among these, tadalafil and sildenafil are also used to treat pulmonary arterial hypertension at recommended doses[33]. Sildenafil was also the first effective and commercially available oral therapy for ED, and by 2019, the broader benefits of PDE-5 inhibitors in treating cardiovascular diseases were beginning to be recognized[34]. Figure 1 provides a summary of the various mechanisms adopted by the PDE-5 inhibitors to improve penile erection.

5.1 Potential Detrimental Effects of PDE-5 Inhibitors

PDE-5 inhibitors such as vardenafil (Levitra), sildenafil (Viagra), and tadalafil (Cialis) have been clinically tested for the treatment of erectile dysfunction[35]. According to the guidelines set out by the European Society for Vascular Medicine, PDE-5 inhibitors are also recommended as an alternative treatment for acute Raynaud's phenomenon associated with systemic sclerosis[36,37]. While all PDE5 inhibitors are mostly tolerated, quite a few patients (over 10%) experience headaches, a common adverse drug reaction (ADR) associated with the vasodilatory properties of the drug[38]. Other known ADRs include rhinitis, dyspepsia, nasal congestion, and dizziness[38]. In 2007, the Food and Drug Administration (FDA) warned about the possibility of adding hearing loss as a potential side effect to the labels of PDE5 inhibitors. Subsequently, there has been evidence suggesting that these inhibitors may be linked with anterior optic neuropathy[31,39].

5.2 Availability, Accessibility of PDE-5 Inhibitors and Limitations of Their Use in ED Treatment

PDE-5 inhibitors are available globally, with sildenafil, vardenafil, avanafil, and tadalafil being the main agents marketed worldwide[34]. However, mirodenafil, lodenafil, and udenafilcan be found in select countries[34,40]. The pharmacokinetics and pharmacodynamics of each agent may vary, influencing the rate of onset, duration of action, and potential side effects[41-43]. Although more selective PDE-5 inhibitors were in development, these trials were suspended, probably because the market is already saturated with agents that have wider cardiovascular benefits, such as endothelin receptor antagonists[31]. As a result of the improved understanding of the broad physiological properties of PDE-5 inhibitors already marketed for ED, further studies are in progress to investigate their potential application in the treatment of other health conditions like intermittent claudication, chronic kidney disease, Raynaud's phenomenon, myocardial infarction, diabetes mellitus, and heart failure[31,34].

Although PDE-5 inhibitors are effective in treating erectile dysfunction, their effectiveness is dependent on endogenous nitric oxide formation[44]. While these drugs maintain intravascular cGMP levels, they do not increase nitric oxide levels. In addition, PDE-5 inhibitors may not be suitable for patients with severe cardiovascular diseases or those taking specific medications[32,35]. However, some patients may experience side effects or may not respond to PDE-5 inhibitors, thereby limiting their use. Similarly, the cost of PDE-5 inhibitors can be high and can vary from country to country[35]. In South Africa, while PDE-5 inhibitors are available, a lack of awareness and social stigma may limit their use[43]. As such, alternative treatments, such as the use of aphrodisiac plants may represent a more acceptable and affordable treatment option for erectile dysfunction.

6. Medicinal Plants in Erectile Dysfunction Treatment

On a global scale, ED prevalence is relatively high and as a result, many individuals have resorted to alternative treatments, such as the use of aphrodisiac plants, which are reported to be efficient, affordable, easily accessible, and have reduced side effects[45]. According to Sandroni[46] and Kotta *et al.*[47], aphrodisiacs can be classified into three groups based on their therapeutic effects. These groups may include (i) those that enhance sexual desire and arousal, (ii) those that improve erectile function, and (iii) those that enhance sexual pleasure[46,47].

Several African medicinal plants from various genera and families are known to have properties of sexual stimulants[48]. Noumi *et al.,*[49] showed that approximately 69 plant species are utilized as aphrodisiacs in Cameroon. Similarly, a survey conducted in Western Uganda found that approximately 31 plant species are

used to treat erectile dysfunction[48]. A review by Ajao *et al.,*[48] further established that 209 plant species from 73 families were used as aphrodisiacs in sub-Saharan Africa. Notably, South Africa with 75 plant species has the highest number of aphrodisiac plants, followed by Uganda, Nigeria, Kenya, Tanzania, and Zimbabwe, with 32, 28, 23, 19, and 17 plant species, respectively[48]. The rich South African biodiversity, which ranks third globally, following Brazil and Indonesia, may explain the abundance of aphrodisiac plants in the country[2].

Traditional medicine has a long-standing and culturally significant heritage in South Africa, with medicinal plants playing a crucial role in traditional healing practice[50]. The majority of the South African population uses medicinal plants to treat several diseases and disorders and has passed this practice through generations[51]. To manage ED and low sexual desire, most men explore traditional treatment options, including medicinal plants[48]. For most people, medicinal plants are the preferred treatment option for managing ED and other ailments because they are natural, affordable, and available with little or no side effects[52,53]. Like many African countries, most South Africans rely on herbal remedies mostly because plants are easily accessible, treatment can be self-administered, and the practice is culturally acceptable in the country[10]. By choosing this treatment option, they avoid several complications associated with healthcare facilities, such as shortage of drugs, long-distance travel, long queues, and many others[54]. The country boasts of great cultural diversity and several ethnic groups, which has resulted in a massive use of medicinal plants across the provinces. Different ethnic groups in South Africa use various plants to treat erectile dysfunction[55,56]. Six South African plants (Figure 2) are known for their use in managing this condition, while their effectiveness is currently being studied. Across the country, the *Vha Venda* people use *Securidaca longepedunculata* and *Wrightia natalensis* plants to treat this disorder[57], whereas the roots of *Eriosema kraussianum* are used by the Zulu people[58]. Although the roots of *E. kraussianum* have been used



Figure 2. South African plants are traditionally used to treat erectile dysfunction. **(A)**. *Tulbaghia violacea*, also known as wild garlic (English), *wildeknoflok* (Afrikaans), *utswelane* (Xhosa), *isihaqa*, and *incinsini* (isiZulu)61. **(B).** *S. longepedunculata*, also known as violet tree (English), *rooipeultjie* (Afrikaans), *mpesu* (tshiVenda), and *iphuphuma* (isiZulu)62. **(C).** *W. natalensis*, also known as saddle-pod (English) or *musunzi* (tshiVenda)63. **(D).** *Eriosema kraussianum*, also known as *uBangalala* (isiZulu). **(E).** *Rhoicissustridentala*, also known as wild grape (English); *isaqoni* (Xhosa); *umthwazi* (isiZulu); *lumbu* (Xitsonga). **(F).** *Bulbinenatalensis*, also known as *rooiwortel* (Afrikaans)

for centuries to treat erectile dysfunction, their safety remains a concern. Five pyrano isoflavones obtained from *E. kraussianum's* rootstock were assessed for smooth muscle relaxation in the penile muscles of rabbit penile[59]. The authors reported an activity close to that of Viagra (85%) in one of the pyranoisoflavones[59]. In another study, Chloroform and ethanol extracts obtained from the roots of *Rhoicissustridentala, S. long pedunculate*, and *W. natalensis* roots were assessed *in vitro* for their potential to induce smooth muscle relaxation in rabbit penile tissues. The results showed a dose-dependent smooth muscle relaxation in all extracts, with the ethanol extracts showing significantly higher inducing ability at both concentrations[60].

6.1 Mechanisms of Action of Medicinal Plants in ED Treatment

6.1.1 Medicinal Plants as Testosterone Boosters

The popularity of herbal products as natural testosterone boosters has surged in recent years, leading to several clinical studies attempting to generate scientific evidence of their efficacy (Table 1)[64-66]. Among the plants, *Panax ginseng* has been examined in multiple clinical studies for its effect on testosterone concentrations[67-70]. However, only one of these clinical studies reported a significant increase in testosterone levels[68]. Fenugreek (*Trigonella foenum-graecum* plant) is another commercially available herb studied for its effect on testosterone concentrations. Some randomized, double-blinded, placebo-controlled clinical studies have shown that fenugreek supplementation can increase testosterone levels[64,71].

Clinical studies have also investigated the effects of ashwagandha KSM-66® (*Withania somnifera* plant) root extract on testosterone concentration[72-75]. Three of the four studies conducted on this herb demonstrated positive effects of *ashwagandha* supplementation on testosterone levels[72,74,75]. GamalEl Din *et al.,*[76] examined the patented extract Trib Gold on testosterone concentration. Trib Gold is a capsule containing 250 mg of *Tribulus terrestris* plant extract manufactured by Nerhadou International[76]. The study by GamalEl Din *et al.,*[76] recruited middle- to older-age men with erectile dysfunction and lower urinary tract symptoms and found that Trib Gold was able to increase testosterone concentration. However, a study by Kamenov *et al.*[77], who also recruited men with erectile dysfunction, found that administration of the *T. terrestris* extracts; using the patented Tribestan (capsule with 250 mg *T. terrestris* extract), which Sopharma manufactures; did not significantly increase testosterone concentration.

Plants used for erectile dysfunction and as aphrodisiacs also show stimulatory effects of testosterone production[78]. *Tulbaghia violacea* Harv. is a plant species indigenous to South Africa and is known for its use as an aphrodisiac. Ethanol extracts of this plant have been shown to increase testosterone production[79]. With the growing number of men seeking natural remedies for erectile dysfunction, there is a need for a natural product with a mechanism of action like that of the PDE-5 inhibitors and capable of stimulating testosterone production to compete against the existing PDE-5 inhibitors.

6.1.2 Modulation of Signaling Pathways

Several signalling pathways have been linked to the regulation of the erectile response, including the erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 pathway and phosphatidylinositol 3-kinase/protein kinase B (Akt)/eNOS/NO pathway[80]. Activation of phosphatidylinositol 3-kinase by shear stress and growth factors leads to phosphorylation of Akt, which in turn phosphorylates eNOS and accelerates the production of nitric oxide (NO)[80]. The medicinal plants, *Panax ginseng* and *Eucommia ulmoides*are believed to function through this mechanism[81]. The activation of the transcription factor Nrf2 promotes the heme oxygenase-1 pathway, which has a major function in the male reproductive system[83]. Medicinal plants such as *Mucuna pruriens* and *Tribulus terrestris* have been identified as activators of this pathway[81]. These signalling pathways offer potential targets for the therapeutic action of medicinal plants for treating erectile dysfunction. *In vitro* and *in vivo* experiments were conducted to evaluate the inhibitory effect of soluble epoxide hydrolase, using a methanol extract from *Moringa oleifera* Lam (MEMO) seeds[82]. In isolated rats, MEMO was found to notably relax the smooth muscle of the corpus cavernosum at concentrations ranging from 0.1 to 100 µg/mL. Additionally, it increased sexual activity, as indicated by intracavernous pressure relative

Table 1. African medicinal plants with potential for erectile dysfunction treatment

Name of the plant	Country	Parts used	Medicinal use	Reference	Results of investigation	Commercialization
Bulbine natalensis (baker), known As*ibhucu* (Zulu), *Rooiwortel* (Afrikaans), *Ingcelwane* (Xhosa)	South Africa	Stem and roots	Sexually transmitted diseases, diabetes, and arthritis	Yakubu and Afolayan[93]	Aqueous extract administered to rats increased testosterone and luteinizing hormone levels.	No commercialization and no clinical trials have been conducted yet
Cyperus esculentus L. (Tiger nut)	African countries and European	Tubers	improve sexual activity and erectile dysfunction	Allouh and Said[97]	Raw powder of *C. esculentus* given to rats increased testosterone levels, and nitric oxide production, and boosted sexual activity	Tiger nuts milk for erectile dysfunction. Tiger nuts raw snack
Epimedium sagittatum called "horny goat weed"	China	Leaves, stem, and flowers	Treatment of cancer, cardiovascular diseases, and erectile dysfunction	Liu *et al.*[98]	Icariin, from *Epimedium sagittatum* given to castrated rats, enhanced NOS expression, increased testosterone levels, and inhibited PDE-5	Horny goat weed tablets are sold in pharmacies. Safety and effectiveness are yet to be confirmed through clinical studies
Tribulus terrestris	African and European countries	Fruit and roots	Treatment of high blood pressure, urinary infections, and low sex desire	Russo *et al.*[99]	Extracts from *Tribulus terrestris* given to rats increased testosterone levels. In a clinical trial, intake of *Tribulus terrestris* tablets for 30 days by patients aged 18-60 with erectile dysfunction and low serum testosterone increased testosterone concentration and improved erectile dysfunction	*Tribulus terrestris* tablets are sold as a libido booster
Ammocharis coranica, known as *Incotho* (Zulu)	South Africa	Roots	Hypertension, cancer, and erectile dysfunction	No records	No records	No records
Gloriosa superba L.	South African and Asian countries	Corms	Erectile dysfunction	Pare *et al.*[100]	Increased testosterone levels and sexual performance	No commercialization and no clinical trials have been conducted yet

to mean arterial pressure, in both normal and diabetic rats[82]. Sahin *et al.,*[83] examined the effects of three herbal extracts, *Mucuna pruriens*, *Tribulus terrestris*, and *Ashwagandha (Withania somnifera)*, on sexual function, reproductive tissue markers, and antioxidant capacity in male rats. The results showed that all three extracts significantly improved sexual function and antioxidant capacity, with *Tribulus terrestris* exhibiting the highest effectiveness. The authors reported that *T. terrestris* demonstrated the most pronounced effects on NF-κB, Nrf2, and HO-1 levels and suggested that the extracts enhance sexual function by activating the Nrf2/HO-1 pathway while reducing NF-κB levels[83].

6.1.3 Inhibition of ED-associated Enzymes

Some medicinal plants attenuate Erectile Dysfunction (ED) by targeting specific enzymes involved in its development[81]. Notably, PDE5 plays a crucial role in the decomposition of cGMP, which is essential for penile erection. Inhibiting PDE5 helps maintain elevated levels of intracavernosal cGMP, enhancing vasodilation induced by Nitric Oxide (NO) and sustaining erection[81]. Synthetic drugs such as sildenafil and tadalafil, also known as oral PDE5 inhibitors, are currently recommended as the primary treatment for ED but can be expensive and may have visual side effects[6]. However, some medicinal plants such as *P. ginseng* and *Eurycoma longifolia* have demonstrated PDE-5 inhibitory properties and show promise as potential sources of novel PDE-5 inhibitors[84]. Furthermore, inhibiting other enzymes, such as arginase and Rho-kinase could offer innovative approaches to ED treatment, although further scientific validation is necessary. Ojo *et al.,*[85] examined how *Ocimum gratissimum* leaves affect enzymes linked with erectile dysfunction. They found that *O. gratissimum* significantly inhibited arginase, acetylcholinesterase (AChE), phosphodiesterase-5 (PDE-5), and angiotensin I-converting enzyme (ACE), in both penile and testicular rat tissues.

6.1.4 Reduction of Oxidative Stress

Reducing oxidative stress is also considered an important mechanism in ED treatment[1]. Medicinal plants such as *Curculigo pilosa, Hunteria umbellata,* and *Microdesmis keayana* have been identified as antioxidants that can help alleviate the oxidative stress associated with ED[86-88]. The effects of *Panax notoginseng* saponins (PNS) on erectile function were investigated in rats with diabetes-induced erectile dysfunction[89]. The results showed that PNS treatment improved erectile function, increased antioxidant levels and increased Akt expression. Electron microscopy studies revealed an improved penile tissue structure in groups treated with PNS compared to the control group. The authors concluded that PNS can improve erectile dysfunction by reducing oxidative stress and restoring penile tissue function[89].

6.1.5 Multiple Mechanisms

The enhancement of sexual performance by medicinal plants has also been linked to multiple mechanisms of action[81]. This assumption lies on the basis that medicinal plants may affect various pathways, making them potentially beneficial for individuals with ED who do not respond to current treatment options. However, in many cases, the specific mechanisms of action of these plants have not been fully elucidated or have only been hypothesized. Several environmental conditions such as temperature, humidity, light intensity and soil composition have an impact on the composition of phytoconstituents in plants and contribute to this complexity[81]. Such factors can strongly influence the type and amount of active substances (secondary metabolites) in medicinal plants. *Epimedium brevicornum* Maxim (EbM) extracts were studied by Chiu *et al.,*[90] for their influence on the relaxation of Corpus Cavernosum (CC) smooth muscle. The authors observed that the extracts stimulated several targets in the NO/cGMP signalling pathway, which caused the CC smooth muscle to relax. They concluded that EbM extracts offer potential as a treatment option for ED after discovering that they improved cGMP production and boosted the relaxing effects of electrical field stimulation[90].

A different study conducted by Fu *et al.,*[91] examined the influence of *Eucommia ulmoides* Oliv. leaf extract (EULE) on ED in diabetic rats and found that after 16 weeks of EULE administration, intracavernosal pressure, Nitric Oxide (NO), and cyclic Guanosine Monophosphate (cGMP) concentrations increased in the experimental rats. The extracts also attenuated oxidative stress, activated the Akt-eNOS pathway,

and enhanced the Hypothalamic-Pituitary-Gonadal (HPG) axis, leading to improved endothelial function and erectile function[91]. These findings suggest that EULE could be a promising therapeutic approach for diabetes-associated ED.

6.2 Efficacy and Safety of Medicinal Plants for Treating ED

Some plants with aphrodisiac properties can affect hormone levels such as Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and testosterone, which help maintain NO levels, essential for erections[92]. For instance, the aqueous stem extract of *Bulbinenatalensis Baker*, when studied in male rats, increased serum testosterone and LH concentrations, leading to enhanced copulatory performance[93]. The authors attributed the enhancement in copulatory performance to the increase in serum testosterone; hence, *the B. Baker* plant is known as a testosterone booster[93]. *Mucuna pruriens*, another promising plant has shown potential for treating both erectile dysfunction and diabetes[94,95]. Its ethanol seed extract improved sexual performance in rats with and without diabetes, reducing blood glucose levels as well[96].

7. Conclusion and Future Research

Erectile dysfunction is a serious condition that affects several male populations worldwide. Despite PDE-5 inhibitors being the most available remedy for the condition, other treatment options could include, lifestyle modifications, injection therapy, psychotherapy, and testosterone therapy. In some cases, especially for men with low testosterone levels, the drug can be combined with testosterone therapy, which have also been known to largely improve the condition. Traditional medicine, involving the use of medicinal herbs and plants is an essential part of healthcare in many low-to middle-income countries, especially South Africa. Medicinal plants are essential in developing countries because of their ease of access and convenience, especially to people living in areas with fewer resources. Several African herbs have been studied for their antimicrobial, anti-inflammatory, antioxidant, and anticancer properties, which could point to their potential in treating various diseases. The numerous beneficial properties found in many of these plants could make them better alternatives, with considerably reduced side effects compared to synthetic drugs. Despite the progress made so far in characterizing these plants for bioactive properties, there is still a need for further studies to assess their efficacy and safety in diverse populations through clinical trials. These studies will provide more information on the benefits of sustained use and potential side effects that may result from prolonged use and over dosage. Furthermore, it is also important to standardize herbal preparations to ensure they are consistent and potent as implied.

In conclusion, though medicinal plants hold great promise in managing erectile dysfunction and other diseases, extensive and interdisciplinary research is needed to understand their full potential. Collaboration between researchers, healthcare professionals, and traditional healers is important to bridge the gap between traditional and orthodox medicines, which will help to improve the quality-of-life of the affected individuals.

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9. References

1. Goldstein I. The mutually reinforcing triad of depressive symptoms, cardiovascular disease, and erectile dysfunction. Am J Card. 2000; 86(2):41-5. https://doi.org/10.1016/S0002-9149(00)00892-4 PMid:10899278
2. 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(1):54-61. https://doi.org/10.1016/S0022-5347(17)34871-1 PMid:8254833
3. Aytaç, Mckinlay, Krane. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. Br J Urol. 1999; 84(1):50-6. https://doi.org/10.1046/j.1464-410x.1999.00142.x PMid:10444124
4. Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, *et al.* Erectile dysfunction. Nat Rev Dis Primers. 2016; 2(1):1-20. https://doi.org/10.1038/nrdp.2016.3 PMid:27188339 PMCid:PMC5027992
5. Castela A, Vendeira P, Costa C. Testosterone, endothelial health, and erectile function. ISRN Endocrino. 2011;

2011:839149. https://doi.org/10.5402/2011/839149 PMid: 22363891 PMCid:PMC3262643
6. Hatzimouratidis K, Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, *et al.* Pharmacotherapy for erectile dysfunction: Recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016; 13(4):465-88. https://doi.org/10.1016/j.jsxm.2016.01.016 PMid:27045254
7. Zaid UB, Zhang X, Lue TF. Physiology of penile erection. Male sexual dysfunction: A clinical guide; 2017. p. 14-21. https://doi.org/10.1002/9781118746509.ch3
8. Ückert S, Oelke M, Stief CG, Andersson K-E, Jonas U, Hedlund P. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. Eur Urol. 2006; 49(4):740-5. https://doi.org/10.1016/j.eururo.2005.12.050 PMid:16460876
9. Mitidieri E, Cirino G, di Villa Bianca RdE, Sorrentino R. Pharmacology and perspectives in erectile dysfunction in man. Pharm Therap. 2020; 208:107493. https://doi.org/10.1016/j.pharmthera.2020.107493 PMid:31991196
10. Moteetee A, Kose LS. Medicinal plants used in Lesotho for treatment of reproductive and post reproductive problems. J Ethnopharmacol. 2016; 194:827-49. https://doi.org/10.1016/j.jep.2016.10.062 PMid:27780751
11. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, Mckinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from the Massachusetts male aging study. J Urol. 2000; 163(2):460-3. https://doi.org/10.1097/00005392-200002000-00015 PMid:10647654
12. Ventegodt S. Sex and the quality of life in Denmark. Arch Sex Behav. 1998; 27:295-307. https://doi.org/10.1023/A:1018655219133 PMid:9604118
13. Pinnock CB, Stapleton AM, Marshall VR. Erectile dysfunction in the community: A prevalence study. Med J Aust. 1999; 171(7):353-7. https://doi.org/10.5694/j.1326-5377.1999.tb123691.x PMid:10590723
14. Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol. 2005; 47(1):80-6. https://doi.org/10.1016/j.eururo.2004.08.017 PMid:15582253
15. Shiri R, Koskimäki J, Häkkinen J, Tammela TL, Huhtala H, Hakama M, *et al.* Effects of age, comorbidity and lifestyle factors on erectile function: Tampere Ageing Male Urological Study (TAMUS). Eur Urol. 2004; 45(5):628-33. https://doi.org/10.1016/j.eururo.2003.11.020 PMid:15082206
16. Pellegrino F, Sjoberg DD, Tin AL, Benfante NE, Briganti A, Montorsi F, *et al.* Relationship between age, comorbidity, and the prevalence of erectile dysfunction. Eur Urol Foc. 2023; 9(1):162-7. https://doi.org/10.1016/j.euf.2022.08.006 PMid:36031560 PMCid:PMC10353735
17. Laumann EO, West S, Glasser D, Carson C, Rosen R, Kang Jh. Prevalence and correlates of erectile dysfunction by race and ethnicity among men aged 40 or older in the United States: From the male attitudes regarding sexual health survey. J Sex Med. 2007; 4(1):57-65. https://doi.org/10.1111/j.1743-6109.2006.00340.x PMid:17081223
18. Berrada S, Kadri N, Mechakra-Tahiri S, Nejjari C. Prevalence of erectile dysfunction and its correlates: A population-based study in Morocco. Int J Impot Res. 2003; 15(1):S3-7. https://doi.org/10.1038/sj.ijir.3900968 PMid:12825102
19. Shaeer K, Osegbe D, Siddiqui S, Razzaque A, Glasser D, Jaguste V. Prevalence of erectile dysfunction and its correlates among men attending primary care clinics in three countries: Pakistan, Egypt, and Nigeria. Int J Impot Res. 2003; 15(1):S8-14. https://doi.org/10.1038/sj.ijir.3900971 PMid:12825103
20. Oyelade BO, Jemilohun AC, Aderibigbe SA. Prevalence of erectile dysfunction and possible risk factors among men of South-Western Nigeria: A population based study. Pan Afr Med J. 2016; 24(1).
21. De Klerk H, De Villiers P, Isaacs S. Prevalence and characteristics of erectile dysfunction in black and mixed race primary care populations of the Cape flats and Helderberg basin area of the Western Cape, South Africa. S Afr fam Pract. 2003; 45(1):14-20. https://doi.org/10.4102/safp.v45i1.2012
22. Lockhat Y, Ross A, Ramlachan P, Rangiah C. The prevalence of erectile dysfunction at a primary healthcare clinic in Durban, KwaZulu-Natal. S Afr fam Pract. 2013; 55(3):289-93. https://doi.org/10.1080/20786204.2013.10874352
23. Nassar GN, Leslie SW. Physiology, testosterone. Treasure Island (FL) StatPearls Publishing; 2018.
24. Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: From basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. Eur Urol. 2007; 52(1):54-70. https://doi.org/10.1016/j.eururo.2007.02.034 PMid:17329016 PMCid:PMC2562639
25. Elkhoury FF, Rambhatla A, Mills JN, Rajfer J. Cardiovascular health, erectile dysfunction, and testosterone replacement: Controversies and correlations. Urol. 2017; 110:1-8. https://doi.org/10.1016/j.urology.2017.07.030 PMid:28774772
26. Becker AJ, Ückert S, Stief CG, Truss MC, Machtens S, Scheller F, *et al.* Cavernous and systemic testosterone levels in different phases of human penile erection. Urol. 2000; 56(1):125-9. https://doi.org/10.1016/S0090-4295(00)00551-3 PMid:10869640
27. Yassin DJ, Doros G, Hammerer PG, Yassin AA. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of

life. J Sex Med. 2014; 11(6):1567-76. https://doi.org/10.1111/jsm.12523 PMid:24712761
28. Park P. Effects of androgens on the expression of nitric oxide synthase mRNAs in rat corpus cavernosum. Br J Urol. 1999; 83(3):327-33. https://doi.org/10.1046/j.1464-410x.1999.00913.x PMid:10233504
29. Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinol. 1999; 140(4):1861-8. https://doi.org/10.1210/endo.140.4.6655 PMid:10098525
30. Kamenov Z. Erectile dysfunction in diabetic men. Sexual dysfunctions: Risk factors, pyschological impact and treatment options. New York: Nova Science Publishers, Inc; 2013. p. 105-38.
31. Jain MS, Koradia SK. Phosphodiesterase-5 (PDE 5) inhibitors in the treatment of erectile dysfunction: A review. Asian J Pharm Res. 2023; 13(1):63-7. https://doi.org/10.52711/2231-5691.2023.00012
32. Dhaliwal A, Gupta M. PDE5 inhibitors. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
33. Montani D, Chaumais M-C, Savale L, Natali D, Price LC, Jaïs X, *et al*. Phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension. Adv Ther. 2009; 26:813-25. https://doi.org/10.1007/s12325-009-0064-z PMid:19768639
34. Tzoumas N, Farrah TE, Dhaun N, Webb DJ. Established and emerging therapeutic uses of PDE type 5 inhibitors in cardiovascular disease. Br J Pharmacol. 2020; 177(24):5467-88. https://doi.org/10.1111/bph.14920 PMid:31721165 PMCid:PMC7707100
35. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. Pharm Ther. 2013; 38(7):407.
36. Fernández-Codina A, Cañas-Ruano E, Pope JE. Management of Raynaud's phenomenon in systemic sclerosis-a practical approach. J Scleroderma Relat Disord. 2019; 4(2):102-10. https://doi.org/10.1177/2397198318823951 PMid:35382396 PMCid:PMC8922649
37. Goldstein I, Burnett AL, Rosen RC, Park PW, Stecher VJ. The serendipitous story of sildenafil: An unexpected oral therapy for erectile dysfunction. Sex Med Rev. 2019; 7(1):115-28. https://doi.org/10.1016/j.sxmr.2018.06.005 PMid:30301707
38. Seftel AD. Phosphodiesterase type 5 inhibitor differentiation based on selectivity, pharmacokinetic, and efficacy profiles. Clin Cardiol. 2004; 27(S1):14-9. https://doi.org/10.1002/clc.4960271305 PMid:15115191 PMCid:PMC6654274
39. Rao AR, Thwaini A, Ahmed HU, Shergill IS, Minhas S. The phosphodiesterase inhibitors and non-arteritic anterior ischaemic optic neuropathy: Increased vigilance is necessary. Br J Urol. 2007; 100(1):3-4. https://doi.org/10.1111/j.1464-410X.2007.06839.x PMid:17488310
40. Andersson KE. PDE5 inhibitors-pharmacology and clinical applications 20 years after sildenafil discovery. Br J Pharmacol. 2018; 175(13):2554-65. https://doi.org/10.1111/bph.14205 PMid:29667180 PMCid:PMC6003652
41. Boettcher M, Nowotny B, Krausche R, Becker C. Evaluation of the influence of sildenafil on the safety, tolerability, pharmacokinetics, and pharmacodynamics of vericiguat in healthy adults. Clin Pharmacokinet. 2023; 62(2):321-33. https://doi.org/10.1007/s40262-022-01203-5 PMid:36729286 PMCid:PMC9998565
42. De Bie FR, Russo FM, Van Brantegem P, Coons BE, Moon JK, Yang Z, *et al*. Pharmacokinetics and pharmacodynamics of sildenafil in fetal lambs on extracorporeal support. Biomed Pharmacother. 2021; 143:112161. https://doi.org/10.1016/j.biopha.2021.112161 PMid:34537676
43. Marais A. The pharmacological management of erectile dysfunction. J Endocrinol, Metab Diab S Afr. 2015; 20(3):4-8. https://doi.org/10.4102/safp.v57i4.4298
44. Toda N, Ayajiki K, Okamura T. Nitric oxide and penile erectile function. Pharmacol Ther. 2005; 106(2):233-66. https://doi.org/10.1016/j.pharmthera.2004.11.011 PMid:15866322
45. Sabiu S, Ashafa A. *Morella serrata* (Lam.) Killick stabilizes biomembrane and rejuvenates sexual competence in male Wistar rats. J Ethnopharmacol. 2017; 205:8-15. https://doi.org/10.1016/j.jep.2017.04.015 PMid:28435048
46. Sandroni P. Aphrodisiacs past and present: A historical review. Clin Auton Res. 2001; 11:303-7. https://doi.org/10.1007/BF02332975 PMid:11758796
47. Kotta S, Ansari SH, Ali J. Exploring scientifically proven herbal aphrodisiacs. Phcog Rev. 2013; 7(13):1. https://doi.org/10.4103/0973-7847.112832 PMid:23922450 PMCid:PMC3731873
48. Ajao A, Sibiya N, Moteetee A. Sexual prowess from nature: A systematic review of medicinal plants used as aphrodisiacs and sexual dysfunction in sub-Saharan Africa. S Afr J Bot. 2019; 122:342-59. https://doi.org/10.1016/j.sajb.2018.08.011
49. Noumi E, Zollo A, Lontsi D. Aphrodisiac plants used in Cameroon. Fitoterapia (Milano). 1998; 69(2):125-34. https://doi.org/10.1016/S0367-326X(98)00025-2
50. Taylor J, Rabe T, McGaw L, Jäger A, Van Staden J. Towards the scientific validation of traditional medicinal plants. Plant Growth Regul. 2001; 34:23-37. https://doi.org/10.1023/A:1013310809275
51. Bhuda MT, Marumo P. African traditional medicine and healing in South Africa: Challenges and prospects before and during Covid 19. Ife Centre Psychol Stud/Serv. 2020; 18:16710.
52. Manukumar H, Kumar JS, Chandrasekhar B, Raghava S, Umesha S. Evidences for diabetes and insulin mimetic activity of medicinal plants: Present status and future

prospects. Crit Rev Food Sci Nutr. 2017; 57(12):2712-29. https://doi.org/10.1080/10408398.2016.1143446 PMid:26857927

53. Masuku NP, Unuofin JO, Lebelo SL. Promising role of medicinal plants in the regulation and management of male erectile dysfunction. Biomed Pharmacother. 2020; 130:110555. https://doi.org/10.1016/j.biopha.2020.110555. PMid:32795922
54. Chinsembu KC. Ethnobotanical study of plants used in the management of HIV/AIDS-related diseases in Livingstone, Southern Province, Zambia. J Evid Based Complementary Altern Med. 2016. https://doi.org/10.1155/2016/4238625. PMid:27069489 PMCid:PMC4812351
55. Semenya SS, Potgieter MJ. Ethnobotanical survey of medicinal plants used by Bapedi traditional healers to treat erectile dysfunction in the Limpopo Province, South Africa. J Med Plant Res. 2013; 7(7):349-57.
56. Buwa-Komoren LV, Mayekiso B, Mhinana Z, Adeniran AL. An ethnobotanical and ethnomedicinal survey of traditionally used medicinal plants in Seymour, South Africa: An attempt toward digitization and preservation of ethnic knowledge. Pharmacogn Mag. 2019; 15(60):115-23. https://doi.org/10.4103/pm.pm_259_18
57. Meyer JM, Rakuambo N, Hussein A. Novel xanthones from *Securidaca longepedunculata* with activity against erectile dysfunction. J Ethnopharmacol. 2008; 119(3):599-603. https://doi.org/10.1016/j.jep.2008.06.018. PMid:18638534
58. Ojewole JA. African traditional medicines for erectile dysfunction: Elusive dream or imminent reality? Cardiovasc J Afr. 2007; 18(4):213-5.
59. Drewes SE, Horn MM, Munro OQ, Dhlamini JT, Meyer JM, Rakuambo NC. Pyrano-isoflavones with erectile-dysfunction activity from *Eriosema kraussianum*. Phytochem. 2002; 59(7):739-47. https://doi.org/10.1016/S0031-9422(02)00035-3 PMid:11909631
60. Rakuambo NC, Meyer JJM, Hussein A, Huyser C, Mdlalose S, Raidani T. *In vitro* effect of medicinal plants used to treat erectile dysfunction on smooth muscle relaxation and human sperm. J Ethnopharmacol. 2006; 105(1-2):84-8. https://doi.org/10.1016/j.jep.2005.10.008. PMid:16309865
61. Afreen S, Syed W, Banerjee S. Herbal based drug discovery for skin and surgical infectious diseases. Biopharmacological activities of medicinal plants and bioactive compounds. 2021; 101.
62. Mongalo NI, McGaw LJ, Finnie JF, Van Staden J. *Securidaca longipedunculata* Fresen (Polygalaceae): A review of its ethnomedicinal uses, phytochemistry, pharmacological properties and toxicology. Journal of Ethnopharmacology. 2015; 165:215-226. https://doi.org/10.1016/j.jep.2015.02.04163.
63. Foden W, Potter L. Wrightia natalensis Stapf. national assessment. Red List of South African plants. Version 2020.1. 2005. http://redlist.sanbi.org/species.php?species=975-1. Accessed on 5 January 2023.
64. Park HJ, Lee KS, Lee EK, Park NC. Efficacy and safety of a mixed extract of *Trigonella foenum-graecum* seed and *Lespedeza cuneata* in the treatment of testosterone deficiency syndrome: A randomized, double-blind, placebo-controlled clinical trial. World J Mens Health. 2018; 36(3):230-8. https://doi.org/10.5534/wjmh.170004 PMid:29623697 PMCid:PMC6119847
65. Aguilar-Morgan AA, Morgentaler A, Reyes-Vallejo LA. Testosterone boosters: How real are their effects? Androg Clin Res Ther. 2022; 3(1):69-76. https://doi.org/10.1089/andro.2022.0007
66. Smith SJ, Lopresti AL, Teo SY, Fairchild TJ. Examining the effects of herbs on testosterone concentrations in men: A systematic review. Adv Nutr. 2021; 12(3):744-65. https://doi.org/10.1093/advances/nmaa134 PMid:33150931 PMCid:PMC8166567
67. Park HJ, Choe S, Park NC. Effects of Korean red ginseng on semen parameters in male infertility patients: A randomized, placebo-controlled, double-blind clinical study. Chin J Integr Med. 2016; 22:490-5. https://doi.org/10.1007/s11655-015-2139-9 PMid:25967606
68. Jung D-H, Lee Y-J, Kim C-B, Kim J-Y, Shin S-H, Park J-K. Effects of ginseng on peripheral blood mitochondrial DNA copy number and hormones in men with metabolic syndrome: A randomized clinical and pilot study. Complement Ther Med. 2016; 24:40-6. https://doi.org/10.1016/j.ctim.2015.12.001 PMid:26860800
69. Kang HY, Kim SH, Lee WJ, Byrne HK. Effects of ginseng ingestion on growth hormone, testosterone, cortisol, and insulin-like growth factor 1 responses to acute resistance exercise. J Strength Cond Res. 2002; 16(2):179-83. https://doi.org/10.1519/00124278-200205000-00003 PMid:11991768
70. Choi Y, Park C, Jang J, Kim S, Jeon H, Kim W, *et al.* Effects of Korean ginseng berry extract on sexual function in men with erectile dysfunction: A multicenter, placebo-controlled, double-blind clinical study. Int J Impot Res. 2013; 25(2):45-50. https://doi.org/10.1038/ijir.2012.45 PMid:23254461
71. Wankhede S, Mohan V, Thakurdesai P. Beneficial effects of fenugreek glycoside supplementation in male subjects during resistance training: A randomized controlled pilot study. J Sport Health Sci. 2016; 5(2):176-82. https://doi.org/10.1016/j.jshs.2014.09.005 PMid:30356905 PMCid:PMC6191980
72. Lopresti AL, Drummond PD, Smith SJ. A randomized, double-blind, placebo-controlled, crossover study examining the hormonal and vitality effects of ashwagandha (*Withania somnifera*) in aging, overweight males. Am J Men's

Health. 2019; 13(2):1557988319835985. PMid:30854916 PMCid:PMC6438434

73. Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract: A randomized, double-blind, placebo-controlled study. Medicine. 2019; 98(37). https://doi.org/10.1097/MD.0000000000017186 PMid:31517876 PMCid:PMC6750292
74. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical evaluation of the spermatogenic activity of the root extract of Ashwagandha (*Withania somnifera*) in oligospermic males: a pilot study. Evid Based Complementary Altern Med. 2013; 2013. https://doi.org/10.1155/2013/571420 PMid:24371462 PMCid:PMC3863556
75. Wankhede S, Langade D, Joshi K, Sinha SR, Bhattacharyya S. Examining the effect of *Withania somnifera* supplementation on muscle strength and recovery: A randomized controlled trial. J Int Soc Sports Nutr. 2015; 12(1):43. https://doi.org/10.1186/s12970-015-0104-9 PMid: 26609282 PMCid:PMC4658772
76. GamalEl Din SF, Salam MAA, Mohamed MS, Ahmed AR, Motawaa AT, Saadeldin OA, *et al*. Tribulus terrestris versus placebo in the treatment of erectile dysfunction and lower urinary tract symptoms in patients with late-onset hypogonadism: A placebo-controlled study. Urol J. 2019; 86(2):74-8.
77. Kamenov Z, Fileva S, Kalinov K, Jannini EA. Evaluation of the efficacy and safety of Tribulus terrestris in male sexual dysfunction - A prospective, randomized, double-blind, placebo-controlled clinical trial. Maturitas. 2017; 99:20-6. https://doi.org/10.1016/j.maturitas.2017.01.011 PMid:28364864
78. 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(2). https://doi.org/10.4103/0973-8258.102825
79. Ebrahim M, Pool EJ. The effect of *Tulbaghia violacea* extracts on testosterone secretion by testicular cell cultures. J Ethnopharmacol. 2010; 132(1):359-61. https://doi.org/10.1016/j.jep.2010.08.018 PMid:20723589
80. Ying A, Yu Q-T, Guo L, Zhang W-S, Liu J-F, Li Y, *et al*. Structural-activity relationship of ginsenosides from steamed ginseng in the treatment of erectile dysfunction. Am J Chin Med. 2018; 46(01):137-55. https://doi.org/10.1142/S0192415X18500088 PMid:29298510
81. Sin VJ-E, Anand GS, Koh H-L. Botanical medicine and natural products used for erectile dysfunction. Sex Med Rev. 2021; 9(4):568-92. https://doi.org/10.1016/j.sxmr.2020.10.005 PMid:33277212
82. Goswami SK, Inamdar MN, Dethe SM, Gururaj GM, Jamwal R, Bhaskar A, *et al*. Erectogenic and aphrodisiac property of *Moringa oleifera*: Involvement of soluble epoxide hydrolase enzyme. Phytother Res. 2016; 30(7):1119-27. https://doi.org/10.1002/ptr.5614 PMid:27020843
83. Sahin K, Orhan C, Akdemir F, Tuzcu M, Gencoglu H, Sahin N, *et al*. Comparative evaluation of the sexual functions and NF-κB and Nrf2 pathways of some aphrodisiac herbal extracts in male rats. BMC Complement Altern Med. 2016; 16:1-11. https://doi.org/10.1186/s12906-016-1303-x PMid:27561457 PMCid:PMC5000417
84. Oboh G, Adebayo AA, Ademosun AO. Phenolic-rich extracts of *Eurycoma longifolia* and *Cylicodiscus gabunensis* inhibit enzymes responsible for the development of erectile dysfunction and are antioxidants. J Basic Clin Physiol Pharmacol. 2018; 29(6):689-96. https://doi.org/10.1515/jbcpp-2017-0160 PMid:29777610
85. Ojo OA, Ojo AB, Oyinloye BE, Ajiboye BO, Anifowose OO, Akawa A, *et al*. *Ocimum gratissimum* Linn. leaves reduce the key enzymes activities relevant to erectile dysfunction in isolated penile and testicular tissues of rats. BMC Complement Altern Med. 2019; 19:1-10. https://doi.org/10.1186/s12906-019-2481-0 PMid:30890127 PMCid: PMC6425690
86. Adefegha SA, Oyeleye SI, Oboh G. African crocus (*Curculigo pilosa*) and wonderful kola (*Buchholzia coriacea*) seeds modulate critical enzymes relevant to erectile dysfunction and oxidative stress. J Complement Integr Med. 2018; 15(4):20160159. https://doi.org/10.1515/jcim-2016-0159 PMid:29791312
87. Oboh G, Adebayo AA, Ademosun AO, Abegunde OA. Aphrodisiac effect of *Hunteria umbellata* seed extract: Modulation of nitric oxide level and arginase activity in vivo. Pathophysiol. 2019; 26(1):39-47. https://doi.org/10.1016/j.pathophys.2018.11.003 PMid:30551914
88. Zamblé A, Martin- Nizard F, Sahpaz S, Reynaert ML, Staels B, Bordet R, *et al*. Effects of *Microdesmis keayana* alkaloids on vascular parameters of erectile dysfunction. Phytother Res. 2009; 23(6):892-5. https://doi.org/10.1002/ptr.2717 PMid:19107738
89. Li H, He W-Y, Lin F, Gou X. Panax notoginseng saponins improve erectile function through attenuation of oxidative stress, restoration of Akt activity and protection of endothelial and smooth muscle cells in diabetic rats with erectile dysfunction. Urol Int. 2014; 93(1):92-9.
90. Chiu J, Chen K, Chien T, Chiou W, Chen C, Wang J, *et al*. *Epimedium brevicornum* Maxim extract relaxes rabbit corpus cavernosum through multitargets on nitric oxide/cyclic guanosine monophosphate signaling pathway. Int J Impot Res. 2006; 18(4):335-42. https://doi.org/10.1038/sj.ijir.3901437 PMid:16395327
91. Fu H, Bai X, Le L, Tian D, Gao H, Qi L-x, *et al*. *Eucommia ulmoides* Oliv. leaf extract improves erectile dysfunction in streptozotocin-induced diabetic rats by protecting

endothelial function and ameliorating hypothalamic-pituitary-gonadal axis function. Evid Based Complement Alternat Med. 2019. https://doi.org/10.1155/2019/1782953 PMid:31467570 PMCid:PMC6699366

92. Malviya N, Malviya S, Jain S, Vyas S. A review of the potential of medicinal plants in the management and treatment of male sexual dysfunction. Andrologia. 2016; 48(8):880-93. https://doi.org/10.1111/and.12677 PMid:27681645
93. Yakubu M, Afolayan A. Effect of aqueous extract of *Bulbine natalensis* (Baker) stem on the sexual behaviour of male rats. Int J Androl. 2009;32(6):629-36. https://doi.org/10.1111/j.1365-2605.2008.00910.x PMid:18710410
94. Seppan P, Muhammed I, Mohanraj KG, Lakshmanan G, Premavathy D, Muthu SJ, *et al*. Therapeutic potential of *Mucuna pruriens* (Linn.) on ageing induced damage in dorsal nerve of the penis and its implication on erectile function: An experimental study using albino rats. Aging Male. 2020; 23(5):313-26. https://doi.org/10.1080/13685538.2018.1439005 PMid:29447059
95. Suresh S, Prakash S. Effect of *Mucuna pruriens* (Linn.) on sexual behavior and sperm parameters in streptozotocin-induced diabetic male rat. J Sex Med. 2012; 9(12):3066-78. https://doi.org/10.1111/j.1743-6109.2010.01831.x PMid:20456630
96. Lampariello LR, Cortelazzo A, Guerranti R, Sticozzi C, Valacchi G. The magic velvet bean of *Mucuna pruriens*. J Tradit Complement. 2012; 2(4):331-9. https://doi.org/10.1016/S2225-4110(16)30119-5 PMid:24716148
97. Allouh M, Said R. Influence of *Ferula Hermonis* acetonic extract on exercise adapted rat gastrocnemius. Austin Cell Biol. 2015; 1(1):1003.
98. Liu WJ, Xin ZC, Xin H, Yuan YM, Tian L, Guo YL. Effects of icariin on erectile function and expression of nitric oxide synthase isoforms in castrated rats. Asian J Androl. 2005; 7(4):381-8. https://doi.org/10.1111/j.1745-7262.2005.00066.x PMid:16281085
99. Russo A, Maisto E, Romis L, Celentano G. Use of a Natural compound made of ecklonia bicyclis seaweed, *Tribulus terrestris* and water-soluble Chitosan Oligosaccharide, in male sexual asthenia with mild or mild-moderate erectile dysfunction and serum testosterone levels at the lower limit of normal. Health. 2016; 8(15):1668-78. https://doi.org/10.4236/health.2016.815162
100. Pare S, Zade V, Thakare V. Evaluation of the potential aphrodisiac activity of aqueous, chloroform and alcohol extract of *Gloriosa superba* in male albino rat. Internat J Theor Appl Sci. 2014; 6(2):39.