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Review

Promising role of medicinal plants in the regulation and management of male erectile dysfunction

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ABSTRACT

Male erectile dysfunction (ED) refers to incompetency to reaching and retaining adequate penile tumescence for sexual intercourse. Over 152 million men globally suffer from ED and by 2025, the number of affected individuals is anticipated to be around 322 million. Pharmacological and nonpharmacological therapies such as phosphodiesterase (PDE) inhibitors, alprostadil, penile prosthesis surgery, and hormonal replacement are available for management and recuperation of ED. Nevertheless, such therapies are reported to have adverse effects as well as life-threatening. Accordingly, diversity of medicinal plant species and bioactive active compounds are preferred as therapeutic options because they are natural, abundant, available, low-cost and cause fewer or no side effects. This current review will emphasise the aetiology, risk factors, mechanisms underlying the pathophysiology of ED, treatments of ED as well as their side effects. It also provides medicinal plants that are proven effective *in vivo* and *in vitro* for the mitigation and treatment of male ED. This knowledge could be used in the future in drug discovery for the development of more natural drugs with no side effects.

1. Introduction

Male erectile dysfunction (ED) or impotence refers to incompetence to reach and retain adequate penile tumescence for sexual intercourse [1]. Over 152 million men globally suffer from ED [1]. The global issue of ED is anticipated to affect around 322 million of males by 2025 [46,47]. Incompetence in accomplishing normal penile erection leads to depression, loss of self-confidence, socialization, and communication with the family [4]. Also, ED leads to conflicts in the relationships that negatively influence the well-being of the couple [5]. ED led men to seek medical care. The fundamental workup for patients with ED includes a detailed history of family, medical, social, and sexual history, helps to disclose the underlying onset of ED. Family history includes diabetes and cardiovascular diseases (CVDs) [6,7]. The medical history includes medications used for depression, mental illness, CVDs, and hypertension [3,41]. Social history should include history of smoking, drug use, alcohol consumption, diet, and exercise [7]. A detailed sexual history includes open-ended questions that require the patient to elaborate more about sexual performance, previous and current relationships, and sexual health status [6,7].

Several validated measures or questionnaires have been developed for use in clinical trial research for ED and to evaluate the efficacy of therapy. The international index of erective function (IIEF) is a 15-items inventory used to evaluate erectile function (6-items), orgasmic function (2-items), sexual desire (2-items), intercourse satisfaction (3-items), and overall satisfaction (2-items). The IIEF is also used to assess

Abbreviations: ACE, Angiotensin-converting enzyme; ACh, Acetylcholine; AChE, Acetylcholinesterase; ADE, Adenosine deaminase; AMS, Aging male's symptoms; Ang I, Angiotensin I; Ang II, Angiotensin II; AT_1R, Angiotensin type 1 receptor; BH_4, Tetrahydrobiopterin; BH_2, Dihydrobiopterin; BMI, Body mass index; cGMP, 3′-5′-cyclic guanosine monophosphate; CVDs, Cardiovascular diseases; CNS, Central nervous system; ED, Erectile dysfunction; EHS, Erection hardness score; EMAS, European Male Ageing study; FSD, Female sexual dysfunction; FSFI, Female sexual functioning index; FAD, Food drug administration; $FADH_2$, Flavin-adenine dinucleotide; FSH, Follicle-stimulating hormone; FT4, Free thyroxine; EDITS, Erectile dysfunction inventory of treatment satisfaction; GnRH, Gonadotropin-releasing hormone; GTP, Guanosine-5′-triphosphate; HCG, Human chorionic gonadotropin; HPLC, High performance liquid chromatography; H_2O_2, Hydrogen peroxide; GAQ, Global assessment question; ICI, Intracavernosal injection; IIEF, International index of erective function; IRS-1, Insulin receptor substrate 1; LSC, Life science checklist; LH, Luteinising hormone; NADH, Nicotinamide adenine; NO, Nitric oxide; NOS, Nitric oxide synthase; O_2^-, Superoxide anion; OH^-, Hydroxyl radical; $ONOO^-$, Peroxynitrite; PI3K, Phosphoinositide-3 kinase; PKC, Protein kinase C; PKG, Dependent protein kinase; PDE, Phosphodiesterase; QEQ, Quality of erection questionnaire; RAS, Renin-angiotensin system; ROS, Reactive oxygen species; SEAR, self-esteem and relationship; SEP, Sexual encounter profile; SEX-Q, Sexual experience questionnaire; SHBG, Sex hormone-binding globulin; SHIM, Sexual health inventory for men; TSH, Thyroid stimulating hormone; UNIFI, University of Florence

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the efficacy of ED treatment [101,102]. The Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) is an 11-items inventory with scores ranging from 0 (lowest satisfaction) to100 (highest satisfaction), has been used to assess satisfaction of patients with treatments for ED [97,98]. The sexual health inventory for men (SHIM) is a scale used to measure the degree of severity of ED (severe, moderate, mild-moderate, mild, no ED) [13]. The erection hardness score (EHS) is 4 score scale used to evaluate the penis erection hardness. The quality of the erection questionnaire (QEQ) evaluates the satisfaction of men with the quality of their erection. The sexual experience questionnaire (SEX-Q) captures the overall sexual experience satisfaction, including couple satisfaction and individual satisfaction [105,106].

Physical examination has been used to evaluate ED patients. Examination includes inspection of secondary sexual characteristics for signs of hypogonadisms such as small testes and penis. Assessment of peripheral pulse for possible signs of tachycardia and bradycardia. Evaluation of penile abnormalities such as Peyronie's diseases, phimosis, and frenulum. Moreover, it measures blood pressure, body mass index (BMI) and waist circumference if not assessed for the past three to six months [6,7,15]. Laboratory testing has been used to assess patients fasting blood glucose, glycosylated haemoglobin (HbA1c), and lipid profile if not assessed within the last 6 months. Hormones test includes early morning total testosterone, bioavailable testosterone, luteinizing hormone, and prolactin. Test results can help to treat factors contributing to ED [6,7,15].

Recently, there are synthetic pharmaceuticals e.g. sildenafil, that has been approved for the treatment of ED. However, these drugs are costly, not easily obtainable and cause many serious health side effects such as dizziness, headaches, heartburn, indigestion, stuffy nose and vasodilatation. As a result of problems associated with synthetic drug usage, many men discontinue the medication and seeking alternative treatments. [6,7]. For these reasons, medicinal plants are used as an option for the management of ED and other complications because they are natural, abundant, available, low-cost and cause fewer or no side effects [18]. Many Africans are reliant on traditional remedies because plants can be easily reached for collection, self-administered, and legal in their culture [19]. The preference for herbal medicines over synthetic drugs is due to problems associated with health care facilities include traveling long distances to hospitals, long waiting lines, absence of laboratory facilities, shortage of drugs, as well as poor attitude of health workers [20]. In addition, plants can be used to develop drugs containing natural compounds [21].

In this current article, we review the aetiology, risk factors, mechanisms underlying the pathophysiology of ED, and treatment of ED including medicinal plants that are scientifically proven for potential mitigation and treatment of male ED. The study will give information that could be used in the future in drug discovery for the development of more natural drugs with no side effects.

2. Views on male erectile dysfunction

2.1. Physiology of the penis

The penis is one of the major parts of the male reproductive system. It consists of three erectile (cavernous) tissues, two corpora cavernosa, and corpus spongiosum. The urethra extended inside the penis to the urinary meatus that opens outside. The deep penile artery and glans or head of the penis are covered with foreskin or prepuce [12–15].

2.2. Aetiology of male erectile dysfunction

2.2.1. Endocrinopathies induced erectile dysfunction

Endocrinopathies such as hypogonadism, diabetes, hyperthyroidism, and hypothyroidism are common endocrine disorders associated with ED [26]. Male hypogonadism is a condition in which the testes fail to produce adequate testosterone [27]. Hypogonadism may result from gonadal disorders called primary hypogonadism or hypothalamic-pituitary dysfunction known as secondary hypogonadism [28]. Low testosterone production has also been found to be associated with type 2 diabetes [29]. The relationship between blood insulin, sex hormone-binding globulin (SHBG), free testosterone, and total testosterone has been reported in the study of Haffner et al. [30], whereby the blood samples of 176 diabetic male patients were compared with controls. Free testosterone, total testosterone, and SHBG concentrations were found lower and insulin levels higher in patients. These were associated with the development of type 2 diabetes in men [30]. This finding was supported by the study of Grossmann and Witter [31], authors have revealed a positive relationship between substantially decreased testosterone levels in type 2 diabetics. In another study, testosterone replacement treatment boosted insulin resistance in diabetic males with low blood testosterone levels [32].

Hyperthyroidism is a medical condition in which the thyroid gland produces abnormally high levels of thyroid hormone [33]. Thyroid-stimulating hormone (TSH) and free thyroxine (FT4) blood tests are commonly used to check that the thyroid gland is functioning normally [34]. Corona and colleagues [35] revealed the correlation between thyroid and ED by using the European Male Aging Study (EMAS) consisting of 3369 men aged ranges 40–79 years and the University of Florence study (UNIFI study) performed at the Andrology and Sexual Medicine Outpatient Clinic comprised of 3203 male patients aged ranges 51.8 ± 13.0 years old. Decreased TSH and increased FT4 were discovered in the EMAS and UNIFI study, 0.3 % and 0.2 %, respectively. Moreover, the study found an association between reduced levels of TSH and ED. Besides, hyperthyroidism increases serum levels of SHBG, thereby reducing the levels of free testosterone concentrations [36].

In terms of hypothyroidism, a study carried out by Chen et al. [34] with 109 ED male patients found that 66.06 % of patients had euthyroid and 29.36 % had subclinical hypothyroidism. Hypothyroidism in ED patients found to be associated with elevated serum prolactin, free thyroxine, and thyroid-stimulating hormone levels compared to patients with euthyroid.

2.2.2. Neurogenic erectile dysfunction

Penile erection is controlled by the autonomic and somatic nervous systems [37,38]. The autonomic nervous system involves the parasympathetic and sympathetic nervous system. The parasympathetic system releasing neurotransmitters includes NO, acetylcholine (ACh), and prostaglandins [38]. The parasympathetic activity results in the relaxation of cavernosal smooth muscle and vasodilation of penile blood vessels. Sympathetic stimulation induces contraction of the penile cavernosal smooth muscle and blood vessels [37,38]. The system releases neurotransmitters such as norepinephrine, endothelin, angiotensin and vasopressin [38].

The somatic nervous system involves sensory nerves and motor nerves carrying signals from the penis (skin and glans) towards the central nervous system (CNS) and from the CNS to the penis during penile erection, respectively [37]. The tactile stimulation of the penis produces neuronal signals transmitted to the erection generating center in the spinal cord, resulting in activation of the autonomic nervous system and subsequently penile erection [37,39]. Neurological disorders impair physiological responses to sexual stimulation. Spinal cord injury, Parkinson's disease, stroke, Alzheimer disease, multiple sclerosis, epilepsy, and pelvic surgery have been found common among patients with ED, which interfere with normal penile erectile function [40–42].

2.2.3. Vasculogenic erectile dysfunction

Normal penile erectile function is dependent on the vascular system supplying blood flow to the erectile tissues of the penis, any impairment results in ED [41]. Vasculogenic ED can be due to atherosclerosis results in occlusion of blood vessels supplying the corpora cavernosa of the penis, hence impairing penile perfusion and subsequent reducing penis

erectile rigidity [37,44]. Endothelial dysfunction plays a key role in the early development of atherosclerosis. Impaired endothelial function occurs due to arterial endothelium injury induced by diabetes and hypertension [43].

2.3. Risk factors for male erectile dysfunction

2.3.1. Diabetes

Diabetes refers to diseases characterized by chronically elevated blood glucose concentration above the normal range due to insufficient insulin or body tissue resistance to insulin hormone [86,87]. Type 1 diabetes and type 2 diabetes are some of the main types of diabetes. Type 1 diabetes accounts for about 10 to 15% of diabetes cases, while type 2 diabetes contributes to approximately 80 % of cases [46]. Type 1 diabetes, also called juvenile-onset or insulin-dependent diabetes is caused by damaged pancreatic-islets β-cells, which synthesize insulin [47]. This is very prevalent in children, but it can now be diagnosed in all age groups. It is an autoimmune disorder in which T lymphocytes destroy islet β-cells [90,91]. The autoimmune response may be caused by exposure to variables such as toxins, diet, and infections [48]. Due to damage, β-cells produce inadequate insulin levels to slow down the blood glucose level, thus leading to hyperglycemia. Because of insufficient insulin, Type 1 diabetic patients rely on exogenous insulin to compensate for the loss of insulin and dietary self-discipline to retain appropriate plasma glucose levels [50].

Type 2 diabetes, well-known as non-insulin dependent and adult-onset diabetes, is defined by abnormal increase in blood glucose levels due to chronic insulin resistance in tissues (muscles, liver, and adipose) and dysfunctional pancreatic β-cells [51]. Type 2 is correlated with family history, age, and the sedentary lifestyle of the patient. Also, it can be due to nutritional factors such an high sugar intake, reduced consumption of fruit and vegetables, as well as elevated diet of red meat and processed meat [93,94].

ED is one of a complication of diabetes. Men with diabetes are almost three times more likely to have ED than non-diabetic males. ED is recorded in 35–90% of men with diabetes [53]. ED becomes severe with aging and the situation also depends on the duration of diabetes [54]. Diabetic males with ED are less responsive to medical therapy compared to non-diabetic males with ED [55].

2.3.2. Hypertension

Hypertension is a serious global medical condition and cardiovascular disease (CVDs) major risk factor affecting 1.39 billion (31.1 %) adult. Approximately 31.5 % and 28.5 % population living with hypertension in low and middle countries, respectively [56]. CVDs have become one of the leading causes of mortality globally, accounting for about 17.3 million cases and by 2030, the prevalence is anticipated to be 23.6 million. CVDs mortality contributes about 8% in both low- and middle-income countries [57]. Stroke, chest pain, heart attack, heart failure, and congenital heart disease are the main causes of death [58].

A strong association between CVDs and ED has been reported. ED has been supposed to be the first symptom of CVDs as it increases the potential for developing CVDs [60,61]. This association has been declared by Uddin et al. [61], and the multi-ethnic study of atherosclerosis conducted on 1757 ED patients without CVDs was followed for a period of 45.6 months. The single Massachusetts Male Aging Study questions were used to evaluate the patients. According to the results, some ED patients developed hard coronary heart disease (CHD) and hard CVD compared to patients without ED (3.4 % hard CHD and 1.4 % without ED, respectively; 6.3 % CVD and 2.6 % without ED respectively). Hard CVD and CHD outcomes evaluated include heart attack, CHD death, resuscitated cardiac arrest, stroke and stroke death [61].

Furthermore, it has been noted that ED and CVDs induced by the same causative factors such as diabetes, tobacco smoking, hyperlipidaemia, obesity, high blood pressure, and sedentary [60,61]. Such risk factors impair endothelial function and lower NO production; therefore, management of these factors will improve ED, preventing associated complications and CVDs [57]. A healthy lifestyle such as daily physical activity, a healthy diet, and minimized alcohol consumption in combination with medication can help reduce blood pressure, recover sexual performance and improve the cardiovascular system [57,64].

2.3.3. Obesity

Obesity is a health condition characterized by an abnormally high body mass index above 30 kg/m^2 [62]. Body mass index (BMI) is the value (kg/m^2) obtained by dividing the body mass or weight (kg) by the body height (m^2). The value is used to assess whether a person has the correct weight for their height. Also, BMI is used to measure whether a person is ≥ 25 kg/m^2 and ≥30 kg/m^2, overweight and obese, respectively [63]. Males with a BMI exceeding 28.7 kg/m^2 showed a 30 % likelihood of developing ED compared to males with normal BMI, which is less than or equal to 25 kg/m^2 [64]. Another study reported that younger men with a BMI of ≥ 30 kg/m^2 (obesity) are prone to ED [63]. It was reported that patients with BMI ≥ 21 kg/m^2 BMI are at increased probability of developing diabetes, high blood pressure and dyslipidemia [64].

Moreover, there is a strong association between diet, obesity, and occurrence of ED [47,67–69]. Men consuming foods that consist of high refine grains, dairy products, red meat, processed meat, too much sugar, and salt, and reduced ingestion of fruits, vegetables, and fish have been found to be at an increased risk of ED [65]. Increased consumption of vegetables, fruits, nuts, whole grains, and fish have been reported in males without ED and decreased intake of such in males with ED. Also, reduced intake of red and processed meat as well as refined grains, are found in males without ED compared to those with ED [67]. Moreover, the study of Ramírez et al. [3] reported poor dietary intake of vegetables and nuts and other lifestyle factors such as tobacco smoking, alcohol ingestion as well and physical inactivity in male patients with ED compared to those without ED. Regular intake of the Mediterranean diet rich in food such as vegetables, fruits, fish, nuts, legumes, and whole-grain is associated with a reduced risk of developing ED [65].

2.3.4. Lack of physical activity

A strong link between sedentary lifestyle and ED has been reported. Physical inactive men are at greater risk of ED than physically active men [68]. Exercise improves sexual function in physically active men; it enhances endothelial NO synthesis, testosterone production,and improves insulin sensitivity and male sexual performance [68]. ED has been found to be closely associated with cardiovascular diseases. The association between the two conditions is linked by factors such as diabetes, high blood pressure, obesity as well and smoking [69]. Usually, patients with ED encounter complications associated with the cardiovascular system and regular exercise improves the cardiovascular system and erection. Moreover, exercise can be prescribed with drugs in the management of ED [70].

2.3.5. Alcoholism

Low levels of alcohol intake are believed to enhance sexual desire and erection. Consumption of alcohol at such an amount relieves anxiety and relaxes muscles. However, drinking large amounts of alcohol suppresses some functions of the central nervous system, leading to decreased sexual desire and ED [1]. It has been reported that excessive alcohol consumption in males causes gonad atrophy, lowering sexual desire and semen quality [71]. Apart from the fact that alcohol inhibits the central nervous system, no significant correlation between alcohol consumption and sexual arousal has been observed in the study by Furukawa [72]. A survey carried out by Connor et al. [73] on both men and women at 38 years of age regarding their history of sexual behaviour due to alcohol intake. Their findings revealed that men (77.4 %) and women (79.9 %) consumed alcohol with their respective partners before sexual intercourse, whereas men (89.2 %) and women (82.1 %)

did not consume alcohol in order to induce sexual activity. Furthermore from this same study, 8.3 % (men) and 7.1 % (women) used alcohol as an enhancer for their sexual performance [73]. Also, it has been reported that incessant abuse or excessive consumption of alcohol contributes to 30–40 % of liver cirrhosis cases globally and even results in death [74]. Liver cirrhosis in male patients results in hypogonadism or a shortage of testosterone by conversion of blood testosterone to estrogen leading to gonad atrophy, loss of sexual desire, impotence and infertility [75].

2.3.6. Cigarette smoking

Tobacco smoking has been found to be associated with ED conditions. Smoking for a short period has been reported to have no significant impact on testosterone levels and erection. However, testosterone concentration may decrease as smokers continue smoking for a longer period [76]. The study by Wen et al. [77] conducted on 18,427 Australian sexually active male and female adults aged ranges from 16 to 69 years. The study discovered that smoking many cigarettes is linked with a higher likelihood of libido and ED. Men who smoke > 20 cigarettes daily have difficulties maintaining erection and lack of sexual interest compared to nonsmokers [77].

Furthermore, cigarette smoking triggers processes leading to the development of atherosclerosis associated with ED [5]. Tobacco smoking also contributes to increased levels of reactive oxygen species, leading to oxidative stress and subsequent endothelial dysfunction and ED [53]. It is believed that stopping cigarette smoking can recover some of the damage that has been caused by tobacco, such as improvements in endothelial function and lowers the probability of developing other cardiovascular-related health problems [5].

2.3.7. Drugs induced erectile dysfunction

Recreational drugs such as cocaine, opioid, and methadone have the tendency to cause ED [25,41]. Cocaine activates endothelin-1 release from endothelial cells. Endothelin-1 is a powerful vasoconstrictor, and its release from endothelial cells causes a decreased production of NO, which is a vasodilator [79]. Opioid use leads to ED by directly suppressing the GnRH or stimulating the release of prolactin at excessive levels in the brain. These, in turn, exert the negative feedback on the release of luteinizing hormone by the pituitary gland and consequent the circulating testosterone levels decreases [83,84]. Methadone stimulates the increased release of prolactin from the brain. Excessive prolactin levels induce inhibition of gonadotropin-releasing hormone secretion, the principal hormone that activates the biosynthesis of testosterone. Hence, testosterone levels vital for sexual function decline significantly [82].

Furthermore, the ED is caused by some prescribed medications commonly used in the treatment of other health-related problems such as depression, mental illness, cardiovascular diseases (CVDs), and hypertension [3,41]. This condition has been seen in patients using drugs such as antihypertensive, antidepressants, cardiac, antipsychotics, and diuretics drugs. Antihypertensive drugs include β blockers, clonidine, methyldopa, verapamil and guanethidine [3,41]. Antidepressants such as tranylcypromine, phenelzine, nortriptyline, sertraline, paroxetine, imipramine, doxepin, fluoxetine, clomipramine, amitriptyline, and citalopram [8]. Cardiac drugs like digoxin, amiodarone [5], beta-blockers, clonidine, hydrochlorothiazide, methyldopa, perhexiline, spironolactone, metronidazole [8]. Antipsychotic drugs include chlorpromazine, lithium, risperidone, and fluphenazine [8]. Diuretics include spironolactone and thiazide [5].

2.3.8. Psychological factors

Men with ED often feel distressed about their problems, have interpersonal problems, and reduced quality of life [83]. ED could be caused by anxiety and depression. A study by Rajkumar and Kumaran [84] revealed the association between depression, anxiety and ED in 64 patients with ED attending clinic. Of the 64 men, 15 (23.4 %) suffer from anxiety disorder, and 8 (12.5 %) men suffered from comorbid depression disorder. Besides, anxiety and depression may result from ED [2,51].

There is strong correlation between female sexual dysfunction (FSD) and male ED. The presence of ED in men has been found to have a significant impact on the women's sexual well-being partners and vice-versa. In the study of Grewal et al. [86], a total of 201 of female subjects and 163 male partners were recruited. Female sexual function was assessed using Female Sexual Functioning Index (FSFI) and male partners was measured by IIEF. The study revealed that 106 (65 %) of males had some degree of ED; 50.9 % had mild ED, 13.5 % had mild-moderate ED, 0.6 % suffer from moderate ED and none with severe ED. The study has also found a positive relationship between IIEF and FSFI scores (35.6 %). Yeoh et al. [87] has also revealed a positive association between men and women sexual functioning in couples who seek medical care from infertility clinic. A total of 150 female patients and 109 husbands were recruited. It was revealed that 17 (11 %) females had sexual dysfunction. The study also revealed strong correlation between FSFI and IIEF total scores ($r = 0.57$). Therefore, it is of paramount importance to involve both male and female partners or spouse in clinical assessment of ED and management [86,87].

3. Sex therapy

Sex therapy has been used for the treatment of ED. The treatment improves confidence, communication, and reduces stress in patients with ED and their partners. The therapy also boosts sexual interest and sexual performance [133,134]. The Depression Anxiety Stress Scale-DASS-2I and the self-esteem and relationship questionnaire are some of the validated tools used to assess patients. The Anxiety Stress Scale-DASS-21, a 21-item self-assessment tool, has been used to measure depression, anxiety, and stress. Item scores ranged from 0 (did not applied to me at all) to 3 (applied to me very much or most of the time). The severity of depression, anxiety, and stress are indicated by scores of 20, 14, and 26, respectively [90]. The self-esteem and relationship (SEAR) questionnaire have 14 questions categorised into 2 domains, the sexual relationship domain (questions 1–8), and the self-confidence domain (questions 9–14). Self-confidence domains include self-esteem (questions 9–12) and overall relationships (question 13–14) [91].

3.1. Mechanisms underlying the pathophysiology of erectile dysfunction

3.1.1. Phosphodiesterase 5 enzyme activity

Penile erection is initiated by sexual excitement, which triggers NO release from the endothelial cells and nervous terminations by nitric oxide synthase (NOS) (Fig. 1). The enzyme NOS uses L-arginine and molecular oxygen as substrates to generate NO. NO then diffuses across the cell membrane into smooth muscles to activate the enzyme guanylyl cyclase. The enzyme, in turn, catalyzes the transformation of guanosine-5′-triphosphate (GTP) into a second messenger, 3′-5′-cyclic guanosine monophosphate (cGMP). Cyclic GMP leads to activation of the cGMP-dependent protein kinase (PKG) step, which phosphorylates proteins that are essential for relaxation. Also, cGMP causes a reduction in intracellular calcium ion (Ca^{2+}) concentrations. The arterial and trabecular smooth muscle relaxation occurs, resulting in arterial dilation, increased blood flow to the penis, and subsequent penis becoming stiffer and more erected [24,25]. The phosphodiesterase 5 (PDE5) enzyme induces inhibition feedback on cyclic GMP, leading to arteriolar vasoconstriction and penile detumescence [93]. However, elevated PDE5 activity results in reduced cGMP levels, thereby ED occurs. Hence, suppressing PDE5 activity improves cGMP levels as well as penile erection [94].

3.1.2. Nitric oxide synthase uncoupling

Reactive oxygen species (ROS) are free radical species containing molecular oxygen [95]. These reactive species are generated as a by-

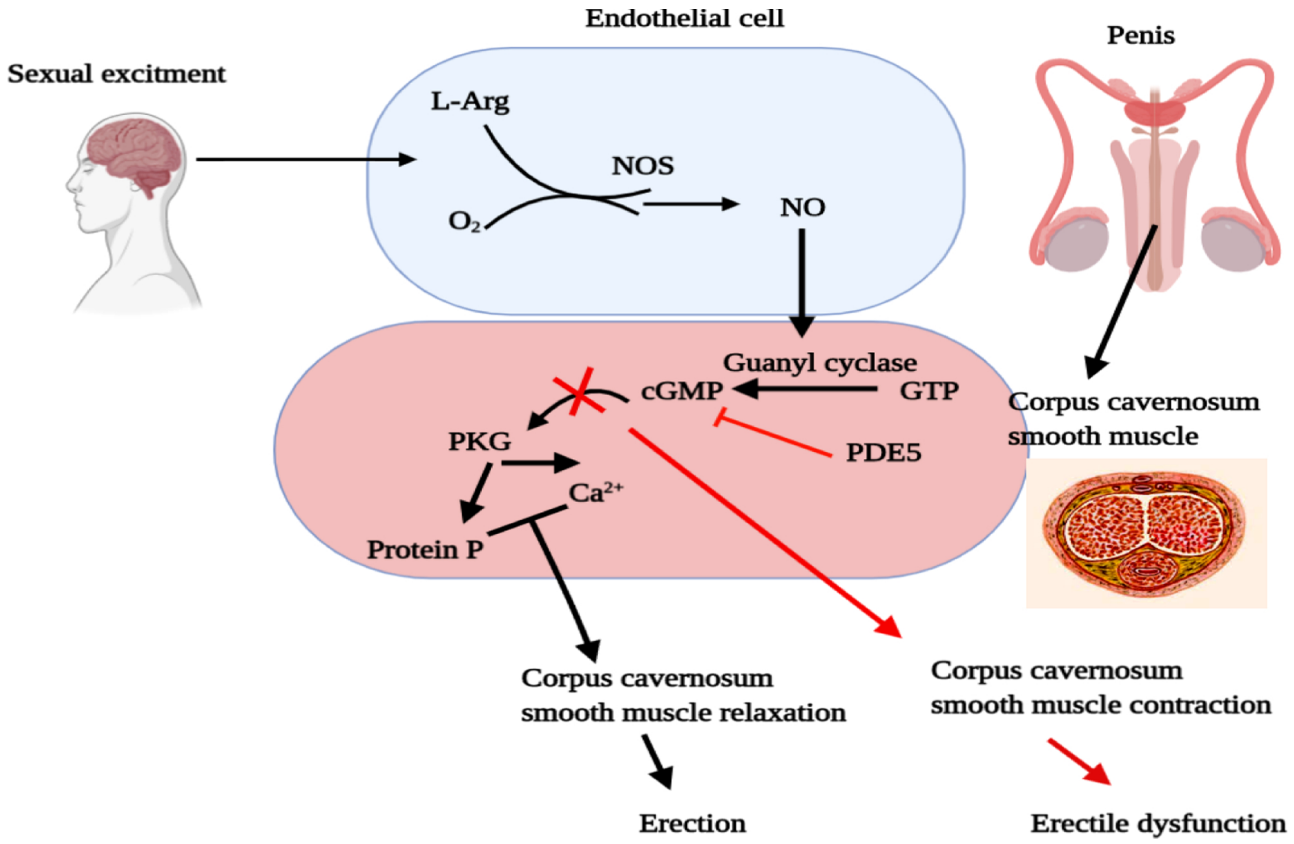

Fig. 1. Phosphodiesterase 5 induces male erectile dysfunction. Abbreviations: L-Arg = L-arginine; O_2 = molecular oxygen; NOS = nitric oxide synthase; NO = nitric oxide; GTP = guanosine-5′-triphosphate; cGMP = 3′-5′-cyclic guanosine monophosphate; PKG = cGMP-dependent protein kinase; Protein P = protein phosphorylation; Ca^{2+} = calcium ion; PDE5 = phosphodiesterase 5.

product of cellular respiration [96], for example, hydroxyl radicals (OH^-), hydrogen peroxide (H_2O_2), and superoxide anions (O_2^-) [97]. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and electron transport chain in mitochondria pathways are major sources of ROS [98]. generating higher amounts of ROS [98,99,101]. Normally, small quantities of ROS modulate ordinary physiological functions involving growth, such as cell cycle progression and proliferation, differentiation, migration, and apoptosis [100]. However, the disproportion between ROS concentration and antioxidant protection mechanism leads to oxidative damage to cells, a condition called oxidative stress [101].

Nitric oxide is a powerful vasodilator and free radical synthesized by the endothelium (Fig. 2). Endothelial NOS synthesizes NO using L-arginine and oxygen molecules as well as tetrahydrobiopterin (BH_4), flavin adenine dinucleotide, flavin mononucleotide and calmodulin cofactors [104,105]. BH_4, the main cofactor in this reaction, has a significant role in the synthesis of NO by NOS. Oxidative stress causes oxidation of BH_4 to dihydrobiopterin (BH_2), thus inducing uncoupling NOS. These uncoupled NOS further generate increased superoxide anions instead of NO, thus bringing about a decline in NO level [106–108]. These are unstable radicals (superoxide and NO), and their reaction forms peroxynitrite ($ONOO^-$), which is a much more stable radical and a strong oxidant. Peroxynitrite further generates powerful oxidants such as hydroxyl and nitrogen dioxide (NO_2) radicals leading to oxidative stress and ED [107,109].

3.1.3. Insulin signaling pathway

Attaching insulin to an insulin receptor on endothelial cells causes phosphorylation of insulin receptor substrate 1 (IRS-1) (Fig. 3). Phosphorylated IRS induces phosphorylation of phosphoinositide-3 kinase (PI3K), and then activation of protein kinase B (Akt). Akt leads to phosphorylation and activation of endothelial NOS. Phosphorylated NOS results in increased NO synthesis and the latter is vasodilation. Nevertheless, insulin resistance leads to activation of protein kinase C (PKC), which in turn reduces the phosphorylation of IRS and inactivation of PI3K. Subsequently, this causes inhibition of NO preproduction and lessens vasodilation [110,111].

3.1.4. Glucose oxidation-induced superoxide production

Hyperglycemia or excessive blood sugar levels lead to increased glucose oxidation (Fig. 4). Glucose oxidation activates the glycolysis pathway, leading to the formation of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), which are used as energy-generating substrates by the electron transport chain of mitochondria. NADH and $FADH_2$, in turn, transfer electrons to complex I – ubiquinone oxidoreductase and complex III – cytochrome c reductase, thereby induce increased superoxide generation [110]. Excessive increased levels of superoxide results in uncoupled NOS and subsequently ED to ED [6–8].

3.1.5. Renin-angiotensin system

The renin-angiotensin system (RAS) plays a pivotal role in the regulation of blood pressure, fluid, and electrolyte balance (Fig. 5). Liver derived angiotensinogen is cleaved by renin, an enzyme released from the kidneys to angiotensin I (Ang I). The angiotensin-converting enzyme (ACE) secreted by lungs catalyzes the conversion of Ang I to potent angiotensin II (Ang II) [113,114]. Ang II, the major component of RAS, induces tonic contraction of the corpus cavernosum smooth muscles during penile erection [113]. However, increased production of Ang II has been found associated with CVDs and ED [114].

Chronic high levels of Ang II causes activation of angiotensin type 1 receptor (AT_1R), thereby promoting sodium and water retention by the

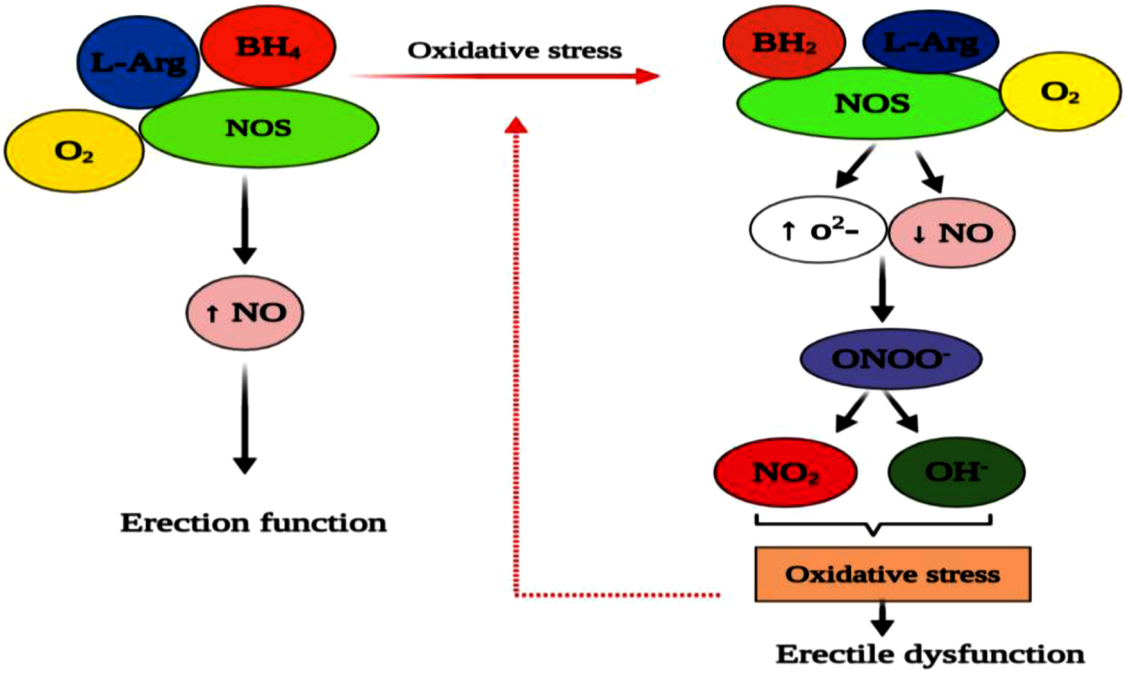

Fig. 2. Oxidative stress induces uncoupling nitric oxide synthase and diminished levels of nitric oxide. Abbreviations: L-Arg = L-arginine; O_2 = molecular oxygen; BH_4 = tetrahydrobiopterin; NO = nitric oxide; BH_2 = dihydrobiopterin; O^{2-} = superoxide; ONOO- = peroxynitrite; NO_2 = nitrogen dioxide; OH- = hydroxyl radical.

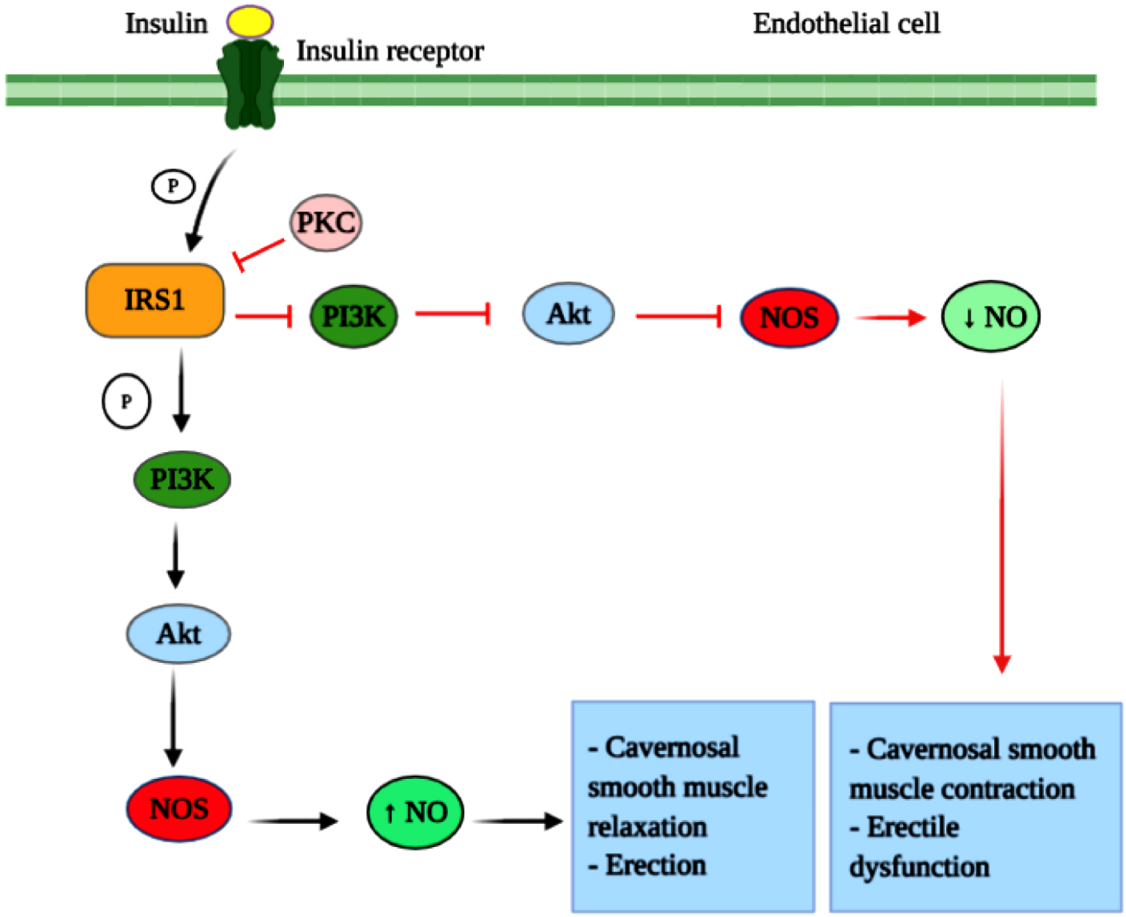

Fig. 3. Relationship between the insulin signaling pathway and the male erectile response. Normal insulin levels result in nitric oxide production, whereas insulin resistance impairs nitric oxide synthesis. Abbreviations: IRS1 = insulin receptor substrate 1; PI3K = phosphoinositide-3 kinase; Akt = protein kinase B; NOS = nitic oxide synthase; NO = nitric oxide; P = phosphorylation; PKC = protein kinase C; line ⊥ = inhibition.

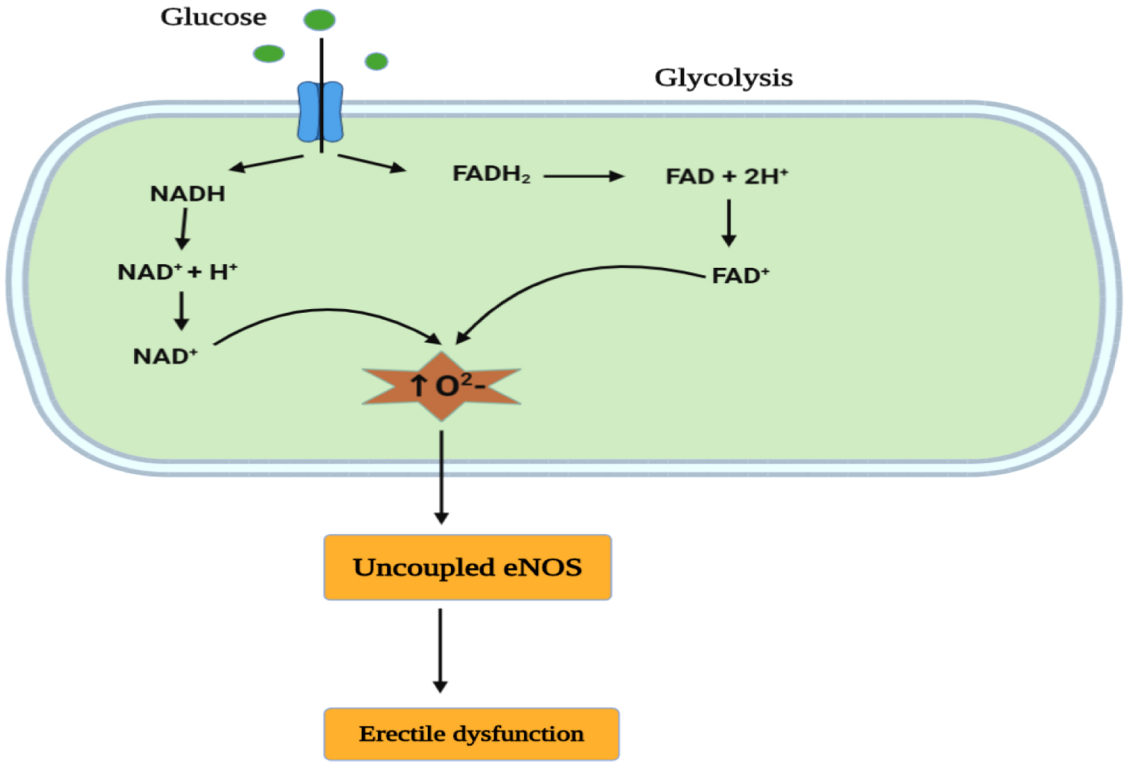

Fig. 4. Sequential steps by which high blood sugar levels lead to increased formation of superoxide anions associated with erectile dysfunction. Abbreviations: NADH = nicotinamide adenine dinucleotide; NAD^+ = oxidized nicotinamide adenine dinucleotide, H^+ = hydrogen ion; $FADH_2$ = flavin adenine dinucleotide; FAD = oxidized flavin adenine dinucleotide; FAD^+ = reduced flavin adenine dinucleotide; O^{2-} = superoxide; ↑ = increased.

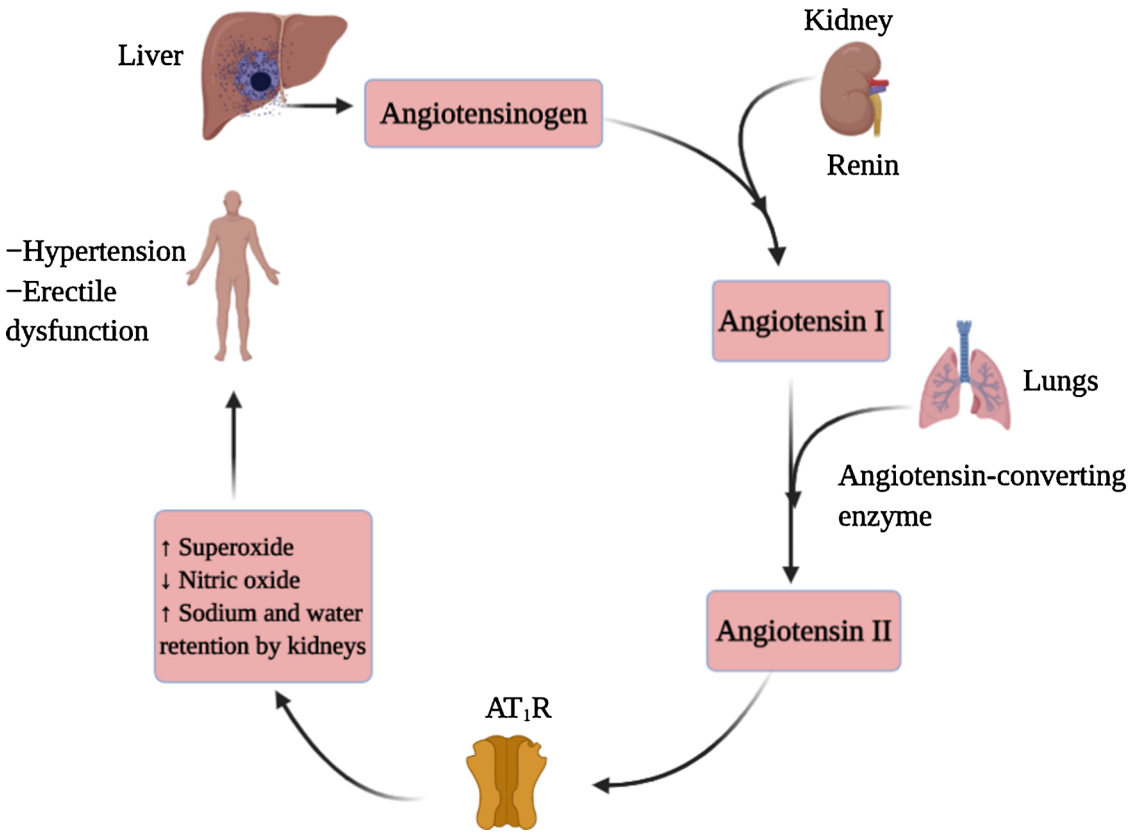

Fig. 5. Chronic effect of increasing levels of angiotensin II in the renin-angiotensin system on penile erection. Abbreviations: AT_1R = angiotensin type 1 receptor.

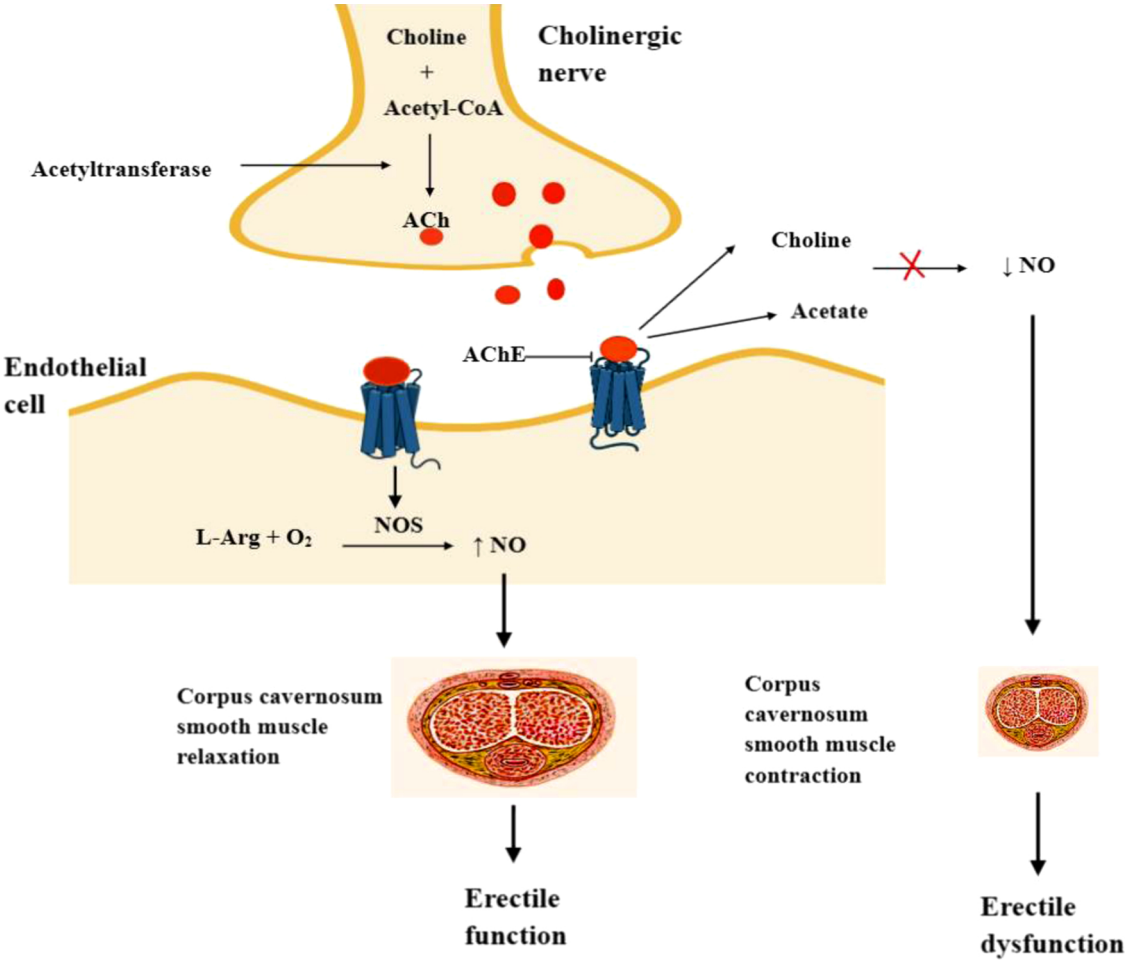

Fig. 6. The effect of acetylcholinesterase on the acetylcholine released by cholinergic nerve leads to contraction of corpus cavernosum smooth muscle compared with absence of acetylcholinesterase results in adequate production of nitric oxide and relaxation effect. Abbreviations: ACh = acetylcholine; AChE = acetylcholinesterase; L-Arg = L-arginine; O_2 = molecular oxygen; NOS = nitric oxide synthase; NO = nitric oxide; ↑↓ = increase or decrease.

kidneys, and vasoconstriction [115], followed by a reduction in endothelial NO concentration, elevated blood pressure and subsequently erectile dysfunction [115,116]. It also stimulate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase results in excessive generation of superoxide anions [117,118]. Hence, treatment with renin inhibitors, ACE inhibitors, and Ang II receptor blockers has been associated with the moderation of Ang II [112].

3.1.6. Acetylcholinesterase pathway

Acetylcholine (ACh) is the parasympathetic neurotransmitter released by the cholinergic nerve within the corpus cavernosum smooth muscle cells of the penis (Fig. 6). ACh induces relaxation of the corpus cavernosum smooth muscle and enhances penile tumescence by stimulating the production of endothelium NO [120,121]. However, the presence of acetylcholinesterase (AChE) decreases the level of ACh by converting to acetate and choline, consequently resulting in ED. Suppression of AChE activity leads to an increased level of Ach, thereby enhancing penile erection [116,120,122].

4. Treatment of male erectile dysfunction

4.1. Phosphodiesterase inhibitors

Phosphodiesterase inhibitors are “first-line” drugs commonly used in the treatment of ED. The United States of Food and Drug Administration (FDA) endorsed about seven PDE5 inhibitors, namely avanafil, lodenafil, sildenafil, udenafil, mirodenafil, tadalafil and vardenafil dysfunction [6,25,123,124]. Their therapeutic effects rely on the mechanism of sexual arousal and penile erection. The drugs are used to maintain an erection, preventing PDE5 enzyme from neutralizing cyclic GMP in such a way that penile erection is prolonged [78].

The PDE5 inhibitors are efficacious in many patients and most patients with ED respond well to drug reactions. The safety, effectiveness and tolerability of PDE5 inhibitors have been assessed in several multicenter double-blind placebo-controlled fixed-dose studies. Goldstein et al. [123] assessed the efficacy and safety of vardenafil in 452 patients diagnosed with diabetes and ED. They were randomized to receive a daily dose of 10 mg, 20 mg vardenafil or placebo for a period of 12 weeks. The IIEF, rates of vaginal penetration, successful intercourse, and global assessment question (GAQ) were used to evaluate the efficacy at the end of 4 weeks. Treatment with both dosages of vardenafil improved the erection, rates of vaginal penetration, and successful intercourse, and GAQ compared to placebo. The study concluded that vardenafil improves ED and can be recommended for patients with diabetes.

Another study conducted by Goldstein et al. [124], randomized a total of 532 men with organic, psychogenic, and mixed ED were randomized to receive various dosages of sildenafil (25, 50, and 100 mg) daily before sexual intercourse for 24 weeks. An additional 32 weeks was granted to those participants who showed minor side effects. The IIEF, successful intercourse and GAQ were also used to assess efficacy. Treatment with sildenafil significantly improved erectile function, successful intercourse, and GAQ score more than placebo. The most

commonly reported side effects include are headache, flushing, and dyspepsia observed in 6–8 % of men. However, 92 % of men further received treatment for an additional 32 weeks. The study concluded that sildenafil is effective and safe for the treatment of ED. Another study, McMurry et al. [125] evaluated the long-term safety and efficacy of sildenafil in men 979 men with ED in 4-year open-label, flexible-dose (25, 50, and 100 mg) sildenafil. Of the 979 men, 584 men continued taking treatment and 395 men discontinued sildenafil treatment due to the cost of sildenafil, adverse effects, and insufficient clinical response. Around 37 (3.8 %) men who participated had experienced one or more adverse effects included headache, dyspepsia, rhinitis, flushing, dizziness, diarrhoea, abnormal vision, nausea, myalgia, hypertonia, mild palpitations, moderate tachycardia, conjunctivitis, respiratory disorder, and photophobia.

Bai et al. [126] revealed the preference, effectiveness and safety of using sildenafil and tadalafil in treating ED in naive men. The study involved 383 men who were grouped to receive 20 mg tadalafil and 100 mg sildenafil for 8 weeks. The IIEF, rates of penetration and successful intercourse were used to assess effectiveness. Both sildenafil and tadalafil treatments improved erection function. Tadalafil was preferred more than sildenafil, 242 (38 %) and 108 (30.9 %), respectively. The preference for tadalafil over sildenafil was due to the longer duration of erection. Headache was reported in > 2% men. The study concluded that both sildenafil and tadalafil are effective and safe.

Zhao et al. [127] examined the efficacy of udenafil in 237 men with ED. Patients were randomized, and double blind to receive daily treatment with udenafil (25, 50, and 75 mg) or placebo for 12 weeks. The IIEF, sexual encounter profile (SEP) diary, and GAQ were used to assess the drug. Administration of a daily dose of 50 mg and 75 mg significantly improved IIEF, SEP diary, and GAQ more than placebo. The most common side effects associated with udenafil intake includes flushing. Another interesting study by Zhao et al. [128] evaluated the efficacy and safety of avanafil in 200 patients with ED. They were randomized and double-blind to receive avanafil (100 or 200 mg) or placebo for a period of 12 weeks. The IIEF, SEP diary, and GAQ to assess the efficacy of the drug. Oral treatment with avanafil significantly improved IIEF erectile function score, SEP, and GAQ compared to placebo. Flushing was the most reported avanafil-related side effect.

Park et al. [129] evaluated the efficacy, safety, and tolerability of mirodenafil for treatment of ED in 122 men with diabetes. Patients were randomized, and double blind to take treatment with mirodenafil (100 mg) or placebo for 12 weeks. The IIEF, SEP diary, GAQ, and the life satisfaction checklist (LSC) were used to assess drug efficacy. Treatment with mirodenafil significantly improved IIEF-EF score, SEP, GAQ, and LSC compared to placebo. The study concluded that mirodenafil is effective as well as tolerable for ED treatment in diabetic patients.

There is also evidence that PDE5 inhibitors could be used in combination with other therapies. Paick et al. [130] assessed the efficacy and safety of mirodenafil in 109 men receiving at least one antihypertensive medication. The participants were randomized, and double-blind to mirodenafil (100 mg) or placebo. The IIEF, SEP diary, GAQ, and LSC were used to assess efficacy. Treatment with mirodenafil significantly improved IIEF-EF score, SEP, GAQ, and LSC compared to placebo. Mild or moderate facial flushing and headache were common in patients. The study concluded that mirodenafil is effective and safe for use in combination with antihypertensive medication. Moreover, Buvat et al. [131] evaluated the safety and efficacy of testosterone on PDE5 in ED patients with low and normal testosterone but not responding to PDE5 inhibitors. A total of 173 men aged ranges 45–80 years participated, of which 138 completed a multicenter, multinational, double-blind, and placebo-controlled study. They were given a dose of 10 mg tadalafil daily for 4 weeks. However, patients failed to respond to tadalafil alone; they were randomized, double-blind, and placebo to receive 1% hydroalcoholic testosterone gel (50 mg/5 g gel). The IIEF and rates of successful intercourse were used to assess efficacy. Administration of testosterone improved erectile function in both groups, testosterone treated and placebo groups over a period of 12 weeks. The study concluded that treatment with tadalafil maybe effective for more than 12 weeks and a combination of testosterone and a PDE5 inhibitor might benefit ED patients, especially those with testosterone levels ≤ 3 ng/mL.

PDE5 inhibitors play important role in reducing the CVDs. Treatment with sildenafil and tadalafil have been found have a cardioprotective effects against cardiac events. The treatment protects against cardiac hypertrophy, myocardial ischemia, duchenne muscular dystrophy, doxorubicin cardiotoxicity, and diabetic cardiomyopathy. Oral intake of sildenafil also improves the cardiac function in myocardial infarction or heart failure patients [130,131]. Sildenafil and vardenafil cause reduction in blood pressure [134]. Cardiovascular events have been reported by patients with comorbid diabetes treated with vardenafil. Moreover, it has been found that vardenafil should not be administered by patients with orthostatic hypotension, and careful with hypertrophic obstructive cardiomyopathy [131,133].

4.2. Alprostadil

Alprostadil or prostaglandin E1 is used as a "second line" in the treatment of ED. There are two forms of alprostadil: intracavernosal injection (ICI) and intraurethral suppository (cream). The treatment is suggested for patients who respond poorly to PDE5 inhibitors and those with drug allergic reactions. Alprostadil stimulates the intracellular adenylate cyclase pathway to synthesize cyclic AMP, leading to relaxation of the cavernosal smooth muscle, thereby penile erection [3,44,124].

The safety, efficacy and tolerability of alprostadil were evaluated in open-label, flexible-dose studies. The effective dose of alprostadil lasting for 60 min was determined for 94 % of the 336 patients (median dose 20 μg, starting from 2.5 to 60 μg) for 6 months and 99 % of injections resulted in satisfactory sexual activity in 272 (82 %) men, and the median remained constant. Patient and partner diaries, and interviews during and after the treatment were used to determine the efficacy and safety of injection. Penile pain, penile ecchymosis, prolonged erection, penile edema, and rash occurred in 71 (21 %) of the men and 11 (3%) had injection site pain. In 21 % of patients with pain, 17 (5%) patients discontinued therapy because of pain. Prolonged erection occurred in 2 (1%) patients and 1 cease therapy following recovery [136].

Another study, conducted with 848 men aged between 18 and 75 years with ED, the effective dose of alprostadil lasting for ≥ 20 min was established for 93 % of patients. The median dose was 20 μg, staring from 2.5 to 60 μg for 6 months. Satisfactory sexual intercourse was reported by men and their partner after 88 % of injections and 90 % of injections, respectively. Side effects have been reported by patients include penile pain (44 %), prolonged erection (8%), priapism (0.9 %), and penile fibrosis (4%). Some patients (3%) discontinued treatment due to pain [137].

4.3. Penile prosthesis surgery

A penile prosthetic or penile implant is used as “third-line” therapy for ED. The surgery involves placing the device inside the penis and scrotum to help men attain and maintain erection. The prostheses are classified as three-piece inflatable, malleable or inflatable, and self-contained hydraulic [124,125]. Surgery is recommended for men, especially those who have an allergic reaction to medications [11]. Some patients reported satisfaction with surgery (81 %); other patients reported disappointments (19 %) because of complications such as infection and erosion in diabetic patients, and urethral injury [138]. Other complications are penile pain, reduced penile length, prosthetic devices are not simple to use, changes occur on sensations during erection and ejaculation, and feeling embarrassed when the implant is visible and not sufficiently rigid [139].

4.4. Gonadotropin replacement therapy

Gonadotropin-releasing hormone (GnRH) is produced from the hypothalamus, and its release results in the production of gonadotropin (FSH and LH) from the pituitary gland. GnRH deficiency leads to a reduction in testosterone level or hypogonadism. Pulsatile GnRH treatment has been approved by the Food and Drug Administration (FDA) for use in patients with hypogonadism [129,130]. Human chorionic gonadotropin (HCG) is synthesized by the placenta in pregnant women and released into the urine. Urine-purified HCG given alone or combined with FSH has been clinically tested effective for use in patients with hypogonadism to induce the production of testosterone [140]. Moreover, exogenous testosterone is another treatment that has been given to patients with hypogonadism to stimulate the biosynthesis of testosterone; however, the therapy has been found to further reduce testosterone levels [28,131]. It inhibits LH and FSH production through negative feedback on the hypothalamic-pituitary-gonadal axis. Besides, the administration of exogenous testosterone results in side effects such as testicular atrophy and azoospermia [28,132].

5. Promising medicinal plants for the treatment of male erectile dysfunction

Plants comprise of an extensive array of phytochemicals, including alkaloids, terpenoids, steroids, and polyphenols [144]. Polyphenols have received more interest among phytochemicals because of their various potential healing effects. Polyphenols are thought to have antioxidant, antibacterial, antiviral, anticancer, antidiabetic, anti-inflammatory, and antimutagenic properties [41,136]. Polyphenols are present abundance in fruits, vegetables, teas, nuts, seeds, wines and coffee [1,41]. Examples of these polyphenols include tannins, phenolic acids, stilbenoids, catechins, procyanidins, and flavonoids [146]. Nevertheless, there is limited research has been on polyphenols to alleviate ED and polyphenols have potential protective effects on the vascular endothelium against ROS damage [1]. Various studies have been done to investigate the medicinal properties of the plants and their mechanism of action for the treatment of male sexual dysfunction.

5.1. Animal testing and in vitro studies

5.1.1. Arctium lappa L

Arctium lappa L. belongs to the Compositae family. It is well-known as burdock (English) and has been used for the treatment of health problems such as sore throat, and dermatitis. The plant has been reported to exhibit physiological health properties such as anti-inflammatory, antiviral, antitumor, and antidiabetic [147]. *A. lappa* has also been used as a sexually stimulating agent as well as for the treatment of infertility and ED [148]. JianFeng [148] investigated the aphrodisiac activities of aqueous root extracts of *A. lappa* (300, 600, and 1200 mg/kg) in Sprague-Dawley adult male rats orally administered for 7 days. Treatment with the extract significantly increased mounting, intromission, and ejaculation frequencies. The extract also significantly increased serum testosterone levels. The study concluded that the aphrodisiac properties of the herbal extract may be attributed to the presence of bioactive compounds such as saponins, lignans, flavonoids, and alkaloids through a multitude of central and peripheral mechanisms. However, there is no clinical study has assessed the safety, effectiveness, and tolerability of *A. lappa* in men with ED.

5.1.2. Anogeissus leiocarpus

Anogeissus leiocarpus belongs to the Combretaceae family. The plant is called African birch [149]. The plant has been used for healing dermatitis, stomach diseases, cough, snake or scorpion bites, and diarrhoea [150], jaundice, inflammation of the liver, headache, toothache, respiratory diseases, diabetic ulcers, jaundice, and syphilis [149]. *A. leiocarpus* has also been used in the treatment of ED. Ademosun et al. [151] investigated the protective effect of *A. leiocarpus* stem bark extract (50 and 100 mg/kg) on antidepressant drug (paroxetine)-induced sexual dysfunction in male adult Wistar rats for a period of 21 days. Treatment with plant extract resulted in inhibition of AChE, PDE5, and arginase activities. Also, the administration of extract significantly improved the antioxidant activity by increasing the levels of nitric oxide. The study concluded that *A. leiocarpus* could be used for the treatment of ED. Till date, there is no clinical study has investigated whether *A. leiocarpus* could have a similar inhibitory effect on AChE, PDE5, and arginase in the treatment of ED in humans.

5.1.3. Asteracantha longifolia (L.) nees

Asteracantha longifolia (L.) Nees belongs to the family Acanthaceae. The plant is used in traditional medicine to cure rheumatic arthritis, kidney infections, jaundice, oedema, gout and as an aphrodisiac. Isoflavone glycoside, stigmasterol, lupeol, fatty acids, and alkaloids were isolated from *A. longifolia* [152]. *A. longifolia* has also been used in traditional medicine as an aphrodisiac. In a study conducted by Chauhan et al. [153], the aphrodisiac activity of *A. longifolia* ethanolic seed extract (100, 150, and 200 mg/kg) in albino male rats. Oral administration for 28 days enhanced copulation in rats substantiated by increased mount frequency (MF) and decreased mount latency (ML) in treated male rats compared to controls. The authors concluded that the results seem to be in agreement with the use of the plant to boost sexual desire. However, there is no clinical research has evaluated the safety, efficacy, and tolerability of *A. longifolia* in men with ED.

5.1.4. Berberine

Berberine is an isoquinoline alkaloid compound most prevalent in several plant species, including *Berberis vulgaris* L [154], *Coptis rhizome*, *Berberis aristana*, and *Phellondendrone amurense* [155]. Berberine has been used medicinally for the treatment of diabetes, obesity, hyperlipidaemia, cardiovascular diseases, and cancer [155]. There are several studies have confirmed the use of berberine in male ED. Chiou et al. [156] established the effect of berberine on the penile erection of New Zealand White male rabbits. The intracavernous injection of berberine (1, 2, 3 and 5 mg/kg body weight) induced increased intracavernous pressure and relaxation of the corpus cavernosum in rabbits. The relaxation effect of berberine on the corpus cavernous is attributable to the endothelial-dependent properties and production of NO by the endothelial cells. It is also attributable to independent properties such as charybdotoxin and 4-AP, the potassium (K^+) channel blockers used as possible mechanisms to ascertain the degree of relaxation effect of berberine on the corpus cavernosum. The authors concluded that berberine has potential to be employed as a natural drug for intravenous injection therapy.

Another study by Tan et al. [157] examined the antioxidant activity of berberine on corpus cavernosum smooth muscle cells in penile ED induced by hydrogen peroxide. In vitro treatment with berberine ($10-1000$ μmol/L) reduced the oxidative damaging effect of hydrogen peroxide on the corpus cavernosum smooth muscle cells isolated from New Zealand male rabbits. It increased the viable cells, NO production, and superoxide dismutase antioxidant enzyme activity [157]. The study concluded that berberine exhibits potential antioxidant properties to prevent penile ED. However, to the best of our knowledge no clinical studies investigating the safety and efficacy of berberine were found in literature. Therefore, future clinical trials based on the berberine effect will help in the development of new drugs that are safe and effective in people.

5.1.5. Bulbine natalensis (Baker)

Bulbine natalensis (Baker) is a member of the family Asphodelaceae. *B. natalensis* is also called rooiwortel (Afrikaans), ibhucu (Zulu) and ingcelwane (Xhosa). *B. natalensis* has been used to heal wounds, rashes, itches, ringworms, chapped lips, stop diarrhoea and vomiting. The plant has been used to manage diabetes, sexually transmitted diseases, and

arthritis [149,150]. Besides, *B. natalensis* has also been used to stimulate sexual intercourse. Yakubu and Afolayan [158] investigated the sexual stimulating effect of *B. natalensis;* oral administration of aqueous extract of *B. natalensis* stem (25, 50, and 100 mg/kg body weight) for a period of 7 days enhanced mating behaviour, penile erection, and increased the levels of blood testosterone and luteinizing hormone in Wistar male rats. The study suggested that *B. natalensis* can be used in the management of ED, improving the lack of libido and sexual disorders. Furthermore, the plant contains tannins, anthraquinones, phenolics, cardiac glycosides, flavonoid, steroids, alkaloids, caffeine, triterpenes, and phlobatannins [158]. Another study by Yakubu and Afolayan [159], oral administration of aqueous extract of *B. natalensis* stem (25, 50, and 100 mg/kg body weight) on days (1, 3, and 7) induced elevation in serum gonadotropin (follicle-stimulating hormone and luteinizing hormone) and testosterone levels, except at higher doses, in male rats. The treatment also induced sexual performance by increasing mount and intromission frequencies. The authors have suggested that *B. natalensis* may be used to recuperate sexual disorders. There have been no clinical trials to support the use of *B. natalensis* to improve ED in human participants.

5.1.6. Camellia sinensis

Camellia sinensis (L.) O. Kuntze is commonly known as tea plant belonging to the family Theaceae. Three forms of *C. sinensis* or teas include green tea, black tea, and oolong tea. *C. sinensis* has been used found to have antilisterial [160] and aphrodisiac properties [161]. The aphrodisiac effect of *C. sinensis* (black tea brewed) was first scientifically validated by Ratnasooriya et al. [161], aqueous tea extract (84, 167, and 501 mg/mL) was administered oral to male rats for about 3 h. The tea extract boosted sexual excitement and copulation. Again, a dose of 84 mg/mL aqueous tea extract was given orally for 30 min. The intake of extract improved the penile erection. Furthermore, oral administration of aqueous tea extract (84 mg/mL) once per day for 3 days increased the serum testosterone concentration in male rats. The study concluded that *C. sinensis* (black tea brewed) is safe and effective and could be used to alleviate sexual dysfunction and as a sex stimulant. Nevertheless, there are no clinical studies have evaluated the safety and efficacy of *C. sinensis* in human subjects.

5.1.7. Cinnamomum cassia

Cinnamomum cassia belongs to the family Lauraceae. Fine powdered *C. cassia* has been used in food preparations as a taste enhancer. *C. cassia* has been used to treat arthritis, diarrhoea, oedema, ED and to enhance sexual [153,154]. Goswami et al. [163] investigated the erectogenic and sexual stimulating properties of methanol extract of *C. cassia* bark in young Wistar male rats. *in vitro* treatment with 50 mg/kg *C. cassia* methanol extract inhibited isolated rat arginase enzyme activity, which plays a vital role in penile erection. Inhibition of arginase activity results in increased levels of arginine in penile smooth muscle and increased levels of cGMP, leading to penile erection. Exposure to *C. cassia* methanol extract (0.1, 1, 10, 1, and 100 μg/mL) induced relaxation of isolated rat cavernous corpus smooth muscle in a dose-dependent manner. Furthermore, oral administration of dose of a 100 mg/kg to young male rats for 28 days improved the smooth muscle level and lessened collagen level in penile tissue. Oral treatment also improved copulation behaviour in male rats. The authors concluded that *C. cassia* could be used to improve ED and the findings support the use of *C. cassia* in Ayurvedic medicine as a sexual stimulant to boost sexual intercourse. However, there are no published clinical researches validated the use of *C. cassia* in mitigating ED. More research should be done to evaluate the safety and efficacy of *C. cassia* extract.

5.1.8. Curcuma longa Linn

Curcuma longa Linn. is a member of the Zingiberaceae family. *C. longa* is commonly called turmeric. It is used medicinally to treat stomach pain, cancer, skin diseases, diabetes, acquired immune deficiency syndrome, blood cleansers, and appetite boosters [164]. The fine powder of turmeric is used in cooking as “spice” [154,155]. Curcumin or diferuloylmethane is a well-known active compound from *C. longa* because of its activity on the penile erectile response [156,157]. Oral administration of pure curcumin (10 mg/kg), water-soluble curcumin (2 mg/kg), and water-soluble curcumin (10 mg/kg) to albino male rats for a period (24 h, 48 h, and 1 week) resulted in significantly increased activity of cavernous tissue cGMP, and heme oxygenase enzyme-1 (HO-1) activity involved in the penile erectile response mechanism [167]. However, there are no clinical trials have investigated whether curcumin has the same effect in humans and has measured the safety and efficacy of curcumin.

5.1.9. Cyperus esculentus L

Cyperus esculentus L. is a member of the Cyperaceae family. *C. esculentus* is well-known as Tiger nut (English) and “Hab Al-zulom” (Arabic) in the Middle East means “the seed of men” [168]. The plant has been used in Ayurvedic medicine as an aphrodisiac to increase sexual activity and improve ED [158,159]. The study of Allouh et al. [168] validated the aphrodisiac activity of *C. esculentus* in adult male rats. Oral intake of 1–2 g/kg of raw *C. esculentus* powder per day for 30 days significantly increased the levels of testosterone in rats and the treatment boosted sexual activity of moderately active rats by increasing the intromission frequency compared to controls. Moreover, the phytochemical screening of the methanol extract of *C. esculentus* using LC–MS indicated the presence of vitamin C, vitamin E, quercetin, and zinc constituents. They are thought to be responsible for the increased serum hormone levels in rats [168]. Another study by Olabiyi et al. [169] adult male rats were fed with a diet supplemented with processed and raw *C. esculentus* (both 10 and 20 %) for 14 days, after the corpus cavernosum was removed and cultured. The results showed that a diet containing 20 % raw plant suppressed the activities of arginase, AChE, and adenosine deaminase (ADE) and increased the production of NO; hence, 20 % raw plant in the diet could improve erectile sexual response. However, there are no clinical studies have been done as yet to assess the safety and effectiveness of *C. esculentus* on ED.

5.1.10. Epimedium sagittatum

Epimedium sagittatum, also called “horny goat weed”, is a natural herb that grows from middle Asia to China. It has been used in the traditional medicines for treatment of cancer, osteoporosis, and CVDs. It has also been used to treat ED [159,160]. Icariin is a well-known compound from *E. sagittatum* believed to be the most effective in the treatment of ED [160–162]. A number of studies have validated the therapeutic effect of *E. sagittatum* icariin in animals. Liu et al. [174] investigated the effect of icariin on ED and NOS isoforms (inducible NOS and neuronal NOS) expression in castrated adult Wistar rats. Oral intake of icariin (1 and 5 mg/kg) causes increased expression of NOS isoforms and inhibition of PDE5. In conclusion, the authors suggested that icariin could be useful in the treatment of ED.

Oral treatment with icariin (50 and 100 mg/kg) for 35 days significantly increased testosterone levels in adult male Sprague-Dawley rats. Treatment with icariin also improved superoxide dismutase activity and diminished malondialdehyde levels [171]. Besides icariin, there are other four compounds (ES01, ES02, ES03a, and ES03b) have been discovered from *E. sagittatum* exhibiting similar PDE5 inhibition effects as sildenafil and tadalafil. The study concluded that *E. sagittatum* could be used to isolate natural compounds to substitutes for synthetic drugs [175]. *E. sagittatum* has demonstrated great potential to improve and treat male ED. Currently, there are no published clinical data assessing the safety and effectiveness of the plant are available.

5.1.11. Ficus capensis

Ficus capensis Thumb is a member of the Moraceae family. *F. capensis* leaves have been used medicinally for centuries for the treatment of diarrhoea, gonorrhoea, ulcer, and male infertility [176]. Akomolafe

et al. [177] investigated the potential anti-ED effects of an aqueous extract of *F. capensis* leaves on penile tissue isolated from male Wistar strain albino rats aged 6–7 weeks old. Incubation of penile tissue in the presence of aqueous extract of F. *capensis* leaves (1:10 wt (w) /volume (v)) reduced the acetylcholinesterase (AChE), angiotensin-I-converting enzyme (ACE), and arginase activity in a dose-dependent manner. The exposure to extract also resulted in the inhibition of NO, and hydroxyl (OH) radicals, chelate F^{2+}, and Fe^{2+} induced lipid peroxidation. Moreover, phytochemical screening of the extract using high-performance liquid chromatography (HPLC) analysis revealed the presence of gallic acid, catechin, chlorogenic acid, caffeic acid, ellagic acid, epicatechin, rutin, quercetin, quercitrin, and kaempferol. The authors concluded that *F. capensis* could be used in the mitigation and treatment of ED [177]. However, there are no clinical trials data available to evaluate the safety and efficacy of *F. capensi* in ED.

5.1.12. Garcinia kola

Garcinia kola is a member of the family Clusiaceae or Guttiferae. *G. kola* is commonly known as bitter kola, male kola, and false kola (English). *G. kola* has been used in the management of diabetes, liver diseases, diarrhoea and sexual dysfunction [162,163]. The plant has also been used traditionally to treat cough, abdominal pain, laryngeal inflammation, and ED [178]. In a study by Sewani-Rusike et al. [178], oral administration of 70 % ethanolic extract of *G. kola* seeds (100, 200, and 400 mg/kg body weight) once per day for 56 days resulted in increased sexual desire, penile erection, serum testosterone concentration, and spermatogenesis in adult Wister male rats. However, there are no clinical trials have now supported its safety and efficacy in mitigating sexual dysfunction, including ED.

5.1.13. Ginkgo biloba

Ginkgo biloba is generally called the Maidenhair tree and Ginkgo [180]. Ginkgo is medicinally used for the treatment of depression and improved ED. It is assumed that Ginkgo stimulates the release of endothelial NO to improve ED. NO, in turn, causes vasodilation and increases blood to the tissues [181]. The sexual stimulating effect of Ginkgo (EGb 761) was established in a previous study by Yeh et al. [182], and incubation of rat isolated Leydig cells with EGb 761 (50, 100, 250, 500, and 1000 μg/mL) for 24 h resulted in significantly increased testosterone production by Leydig cells at 1000 μg/mL. Oral administration of EGb (50 mg/kg) Long-Evans male rats for a period of 28 days and 100 mg/kg for 14 and 21 days resulted in increased mating performance (intromission frequency). However, no changes were observed after 28 days in the levels of serum testosterone, dopamine, and copulation. Besides, a rise in dopamine levels was noted at 50 mg/kg body weight, which was thought to be responsible for copulatory behaviour at this concentration. However, no clinical studies have been conducted as yet to determine Ginkgo safety and efficacy in humans and if it has a similar mechanism of action as in animal experimentation.

5.1.14. Gloriosa superba L

Gloriosa superba L. is a member of the Liliaceae family. The plant has been used as a medicine to cure gonorrhoea, rheumatic arthritis, erectile dysfunction, dermatitis, leprosy, ulcers, gout and snake bites [183]. Colchicine and colchicoside alkaloids are two key constituents isolated from *G. superba*; they heal gout and induce muscle relaxation, respectively [168,169]. The aphrodisiac effect of *G. superba* tuber was revealed in an early study by Pare et al. [185]. The dried crude extracts of water, chloroform, and alcohol of *G. superba* stem and leaves were resuspended in water (water crude extracts) and olive oil (chloroform and alcohol crude extracts). Oral administration of aqueous and olive oil *G. superba* extract (100, 250, and 500 mg/kg body weight per day) for 15 days resulted in increased blood testosterone levels and copulating performance in male albino rats. Moreover, bioactive compounds such as alkaloids, saponins, and steroids were isolated from *G. superba* [185]. There are no published clinical trials that support and assess the safety and efficacy of *G. superba* aphrodisiac activity enhances testosterone production, penile erection, and sexual performance in males.

5.1.15. Hunteria umbellata

Hunteria umbellata belongs to the Apocynaceae family. The plant is used in folk medicine for the treatment of anaemia, diabetes, oedema, managing obesity and male infertility [186]. The effect of *H. umbellata* extract on the enzymes induced by ED has been validated in the study by Oboh et al. [119]. Treatment with *H. umbellata* (50 and 100 mg/kg body weight) for 28 days using adult Wistar albino male rats resulted in significantly decreased activity of PDE5, ACE, and AChE compared to control in isolated corpus cavernosum. In another study, the administration of *H. umbellata* (100, 200, and 400 mg/kg body weight) daily to Wistar male rats for 60 days induced dose-dependent increases in serum levels of LH, FSH, and testosterone. The study concluded that *H. umbellata* could be used to alleviate ED [186]. There are no clinical studies have investigated the safety and efficacy of *H. umbellata*.

5.1.16. Massularia acuminata

Massularia acuminata belongs to the family Rubiaceae. *M. acuminata* is used as an aphrodisiac. The aphrodisiac activity of *M. acuminata* was reported in a previous study by Yakubu and Akanji [187] that the oral administration of aqueous extracts of *M. acuminata* stem (250, 500, and 1000 mg/kg body weight) once per day for 5 days increased libido, copulation as well and substantially increased serum testosterone concentration in *Rattus norvegicus* male rats. Besides, the phytochemical screening of aqueous extract of *M. acuminata* displayed flavonoids, saponins, tannins, anthraquinones, alkaloids, and phenolics. Hence, the sexual stimulating effect of plant extract has been thought to be associated with the presence of these compounds. In addition, bioactive compounds possess androgenic and antioxidant properties [188]. Currently, there are no clinical studies investigating the safety and efficacy of *M. acuminata* found.

5.1.17. Microdesmis keayana

Microdesmis keayana J. Léonard is a member of the family Pandaceae. *M. keayana* has been used as an aphrodisiac to enhance sexual arousal and activity [189]. The sexual stimulating activity of aqueous root extract of *M. keayana* and its isolated alkaloids constituent was demonstrated in a previous study by Zamblé et al. [189]. Oral administration of aqueous root extract of *M. keayana* at a dosage of 150 mg/kg body weight and pure alkaloids at a dose of 3 mg/kg body weight for about 2 h increased the mating performance in Wistar male rats. *M. keayana* is a vasodilator that induces vascular relaxation by initiating the production of NO needed for penile erection; hence, this could be due to presence of alkaloids. No data are available on the clinical trials exploring the safety and effectiveness of *M. keayana* extract.

5.1.18. Moringa oleifera Lam

Moringa oleifera Lam. popularly known as a drumstick is a member of the family Moringaceae. The aqueous leaf extract of *M. oleifera* revealed the presence of active compounds such as gallic acid, catechin, chlorogenic acid, ellagic acid, epicatechin, rutin, quercitrin, quercetin, isoquercitrin and kaempferol using HPLC analysis [190]. The possible aphrodisiac properties of *M. oleifera* on stress-induced ED have been demonstrated in a previous study using male rats. Wistar male rats were given oral doses of *M. oleifera* extract (10, 50, and 250 mg/kg) for approximately 45 min before they were exposed to stress for 7 days. The levels of PDE-5 and testosterone were measured using appropriate kits and mating behaviour was assessed using video. The plant extract slows down the action of PDE-5, the improves blood testosterone concentration and mating performance. The extract also stimulated an increased number of testicular Leydig cells and spermatogenesis [191]. In another study, oral administration of aqueous seed extract of *M. oleifera*

(100, 200, and 500 mg/kg) per day for 21 days increased libido and copulation in male albino rats [192]. No data are available on the clinical studies investigating the safety and efficacy of *M. oleifera* extract.

5.1.19. *Myristica fragnans*

Myristica fragnans, commonly known as Nutmeg, is a member of the family Myristicaceae. Fine powdered Nutmeg is used as an herb in food preparations and medicinally to heal stomach pain, diarrhoea, and rheumatoid arthritis. It has also been reported that Nutmeg possesses aphrodisiac effects [193]. A recent study by Odubanjo et al. [94] showed that the Nutmeg adult Wistar strain albino male rats oral administration of seed extract (100, 200, 300, and 400 μg/mL) suppressed the activities of PDE-5, arginase, AChE, ACE a and iron III oxidative damage in penile tissue. This study suggests that Nutmeg seeds could be used in manage ED. Also, the phenolic compounds such as gallic acid, chlorogenic acid, caffeic acid, catechin, ellagic acid, epicatechin, rutin, quercetin, isoquercitrin, quercitrin, and kaempferol were isolated from aqueous extracts using high-performance liquid chromatography (HPLC-DAD) analysis [94]. To date, no clinical trials have evaluated the safety and effectiveness of Nutmeg have been found at present.

5.1.20. *Ocimum gratissium linn*

Ocimum gratissium Linn is a member of the Lamiaceae family [120]. The plant is used medicinally to cure headaches, stomach pain, diarrhoea, influenza, sore throat, fever, and dermatitis [194]. The plant is used in the alleviation of male sexual dysfunction and the activity of *O. gratissium* on male sexual function was validated in the study conducted by Ojo et al. [120] revealed that exposure to aqueous extract of *O. gratissium* leaves (20–100 μg/mL) reduced the activities of arginase and acetylcholinesterase (AChE) enzyme on the penile and testicular tissues obtained from Wistar male rats. At present, there are no clinical trials have confirmed the safety and efficacy of *O. gratissium* are available.

5.1.21. *Pseudopanax arboreus*

Pseudopanax arboreus is called five fingers (Cameroon) belongs to the family Araliaceae. *P. arboreus* has biological health properties such as anti-inflammatory, antioxidant [195] and aphrodisiac properties [196]. A recent study by Besong et al. [196] reported that the oral administration of methanol extract of *P. arboreus* leaves (46.5 and 93 mg/kg body weight) for 21 days causes considerably increased testosterone levels, testicular weight, and mount and intromission frequencies in adult Wistar strain male rats. Also, the extracts stimulated increased testosterone synthesis. The authors concluded that the aphrodisiac effect of the plant extract might be due to the androgenic activities of flavonoids, alkaloids, saponins, steroids, tannins, and triterpenoids. However, no clinical studies investigating the safety and efficacy of use of *P. arboreus* are available.

5.1.22. *Telfairia occidentalis*

Telfairia occidentalis belongs to the Cucurbitaceae family. *T. occidentalis* is popularly known as fluted pumpkin (English). The plant is used to treat spasm, anaemia [197], cancer, diabetes, malaria, and infertility [198]. The potential effect of *T. occidentalis* seed against ED has been shown in the study of Ademiluyi et al. [118], cultured corpus cavernosum isolated from adult Wistar albino male rats with water extract of pumpkin seed (2–50 μL) induced inhibition of arginase, AChE, ACE, and PDE5, markers of ED. No data on clinical trials have been published to assess the safety and efficacy of use of *T. occidentalis* for ED.

5.2. Clinical studies

5.2.1. *Crocus sativus L. - Saffron*

Saffron is a dried red stigma from *Crocus sativus* L. commonly used as spice and aphrodisiac, and to treat ED [193,194]. A clinical study by Shamsa et al. [200] examined the efficacy of *C. sativus* saffron in 20 male patients aged between 26 and 62 years with ED. Patients received a daily 200 mg saffron tablet each morning for 9 days and a double dose of saffron on day 10. The nocturnal penile tumescence test and IIEF were used to measure efficacy. Treatment with saffron significantly improved tip rigidity, tip tumescence, base rigidity, and base tumescence as well as IIEF score. Another clinical study investigated the effects of saffron gel on ED in diabetic men; 50 men patients were randomized to receive saffron gel or placebo. The IIEF was used to measure the efficacy before and after 1 month of treatment. Saffron gen significantly improved ED. The study suggests that saffron could be used as a treatment for ED in diabetic men. Further research including a large number of participants is required to determine its safety and efficacy.

5.2.2. *Eurycoma longifolia Jack*

Eurycoma longifolia Jack belongs to the Simaroubaceae family. It is popularly known as the Tongkat ali. It has been used to mitigate infertility, as an adaptogen, and ex energy booster [201,202]. Several clinical studies have shown that Tongkat ali improves erectile function by boosting sexual desire and testosterone production [95,201].

In a clinical study by Tambi et al. [204], a daily dose of 200 mg (2 capsules with 100 mg) of Tongkat ali extract were given to 76 male patients aged ranges between 28 and 70 years with low-onset hypogonadism and hypogonadism for a period of 1 month. Aging male's symptoms (AMS) rating scale and blood testosterone levels were used to assess the patients. Intake of Tongkat ali resulted in improved AMS of patients (71.7 % no complaints) and 90.8 patients had normal testosterone levels (6–30.0 nM). Low testosterone levels were considered < 5.99 nM. Another clinical study, a dosage of 200 mg (1 tablet) per day of freeze-dried water extract of *E. longifolia* (Physta) was given to 26 healthy male participants aged ranges between 40 and 65 years for 12 weeks. Physta treatment improved sexual performance, including erectile function, in participants compared to placebo. Further clinical research with a larger number of participants is required to determine its safety and effectiveness.

5.2.3. *Panax ginseng*

Panax ginseng belongs to the Araliaceae family. *Panax* refers to "all healing" [205]. The root and rhizome extract of the plant is consume as an aphrodisiac to stimulate penile erection and sexual intercourse [182,183]. The aphrodisiac activity of ginseng was showed in the study of Choi et al. [206]. Patients with ED were recommended to take tablets of standardized Korean ginseng berry (SKGB) 4 times a day, each tablet containing 350 mg of ginseng extract for 8 weeks. Penile response and early ejaculation were measured at the end of weeks four and eight, respectively. According to the results, ginseng caused a slight change in penile erection and improved early ejaculation. The results confirmed that ginseng can be used to alleviate male sexual functions [206]. Another clinical trial, Andrade et al. [208] evaluated the efficacy of Korean Red Ginseng (KRG) for the treatment of male ED in 60 patients with mild or mild moderate ED in a double-blind placebo-controlled study. Patients were randomized to receive 1000 mg of KRG three times a day and placebo. The IIEF was used to measure efficacy. Treatment with KRK significantly improved the IIEF score of erection in 20 patients (66.6 %) and GAQ compared to placebo. Further research with a large number of participants is needed to affirm its safety and efficacy.

5.2.4. *Tribulus terrestris*

Tribulus terrestris (TT) is a member of the family Zygophyllaceae. TT has been used medicinally to cure a range of health-associated problems such as high blood pressure, stomach problems, and urinary infections [209]. The plant has also been used to boost male sexual desire and mating behaviour [189,190]. Gauthaman et al. [211] investigated the androgenic properties of TT extract in primates, and intravenous administration of TT extracts (7.5, 15, and 30 mg/kg) for 8 weeks induced

increased plasma testosterone, dihydrotestosterone, and dehydroepiandrosterone sulphate, especially at a dose of 7,5 mg/kg body weight. Oral administration of TT extract (2.5, 5, and 10 mg/kg body weight) in rabbits and rats resulted in increased dihydrotestosterone levels at a dosage of 5 and 10 mg/kg body weight. Protodioscin, a saponin like compound, was isolated from the TT extract and this was believed to elicit the release of luteinizing hormone from the pituitary gland, which in turn activates the synthesis of testosterone by Leydig cells.

A clinical trial, daily oral intake of 30 tablets of TT (450 mg) for 30 days by patient age ranged between 18–45 years, 46–49 years, and > 60 years with ED and serum testosterone levels (280 ng/dl and 350 ng/dl) resulted in considerably increased serum testosterone concentrations in all age groups and improved ED in patients with mild or moderate ED [212]. The authors concluded that TT maybe safe and effective for use in the alleviation of sexual desire and erectile function. However, further clinical trials with larger sample sizes are needed to evaluate its safety and efficacy before it can be recommended to patients for treatment.

5.2.5. Yohimbine

Yohimbine is a nitrogenous organic compound derived from *Pausinystalia Yohimbe* (K. Schum.) Pierre [213]. Yohimbine is used therapeutically to treat ED and to enhance sexual intercourse [214]. Yohimbine has been tested in clinical trials. The efficacy and safety of Yohimbine was established in the study of Guay et al. [215] using 18 male patients with ages ranging from 34 to 69 years. A dose of 5.4 mg Yohimbine hydrochloride was given orally three times daily for 4 weeks and 10.8 mg dose for another 4 weeks. Following the Florida sexual health questionnaire, blood tests, and nocturnal penile tumescence and rigidity monitoring were used to screen the patients. Higher sexual questionnaire scores, slightly increased serum testosterone, and significantly improved penile rigidity were observed in patients with less severe ED. Minimal side effects were observed in two patients, one had mild hot flashes and another mild anxiety. Yohimbine had no effect on blood pressure or pulse rate. The authors concluded that Yohimbine is effective for the treatment of ED, particularly in some men with organic ED. There have been no further clinical trials with a large group of people are needed to confirm its safety and efficacy before FDA approval.

5.2.6. VigRx plus

VigRx plus is formulation with blend of natural herbs such as *P. ginseng*, *G. biloba*, *Serenoa repens*, *Crataegus laevigata*, *Ptychopetalum olacoides*, *Erythroxylum catauba*, *Cuscuta chinensis*, *E. sagittatum*, *T. terrestris*, *Turnera diffusa*, and Bioperine®. VigRx (VXP) is used to improve erectile function. Shah et al. [216] evaluated the safety and efficacy of VigRx (VXP) in 78 men aged 25–50 years with mild and moderate ED in a double-blind placebo-controlled study. Patients were randomized to receive a dose of 2 capsules twice per day of VXP or placebo for 12 weeks. The IIEF and EDITS were used to assess efficacy. VXP significantly improved erection function. Mild severity fever (2.3 %) was the most common adverse event. Tolerability was rated as good. No data have been found in other clinical trials with a large sample size that determine its safety and efficacy.

6. Conclusion

ED is a complex disorder involving several pathophysiologic mechanisms such as nitric oxide synthase, insulin resistance, glucose oxidation-induced superoxide production, renin-angiotensin system, and acetylcholinesterase. Owing to the side effects resulting from usage of PDE inhibitors, alprostadil, penile prosthesis and hormonal replacement therapies excited prompted researchers' interest to investigate more medicinal plant species and natural active constituents to alleviate and cure ED. Few clinical trials have evaluated the safety and efficacy of medicinal plants for the treatment of ED. According to the results of animal experiments and in vitro studies, medicinal plants have revealed potential therapeutic effects against male ED. Clinical trials on these medicinal plants could help in the development of new and abundant drugs for ED treatment.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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