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Male sexual dysfunction: A review of literature on its pathological mechanisms, potential risk factors, and herbal drug intervention

Lei Chen[a,1], Guang-rui Shi[b,1], Dan-dan Huang[c], Yang Li[d], Chen-chao Ma[e], Min Shi[a], Bin-xiao Su[f,*], Guang-jiang Shi[g,*,1]

[a] Medical College of Xi'an Pei Hua University, Shaanxi Xi'an 710125, China
[b] Joint Laboratory of Traditional Natural Medicine, Yunnan Minzu University, Kunming, 650500, China
[c] Department of pharmacy, The Second Affiliated Hospital of Fujian Medical University, Fujian, 362000, China
[d] College of Life Science, Northwest University, Shaanxi Xi'an 710069, China
[e] Department of Pharmacy, Xi Jing Hospital, Air Force Medical University, Shaanxi Xi'an, 710032, China
[f] Department of Anesthesiology, Xi Jing Hospital, Air Force Medical University, Shaanxi Xi'an, 710032, China
[g] Department of Pharmacology, China Pharmaceutical University, Nanjing, 211198, China

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ABSTRACT

Sexual dysfunction (SD) is a disorder of sexual behavior and sexual sensation that appears as an abnormality or absence of sexual psychology and physiological reaction. It is a general term for many different symptoms includes several aspects, erectile dysfunction (ED), failure of sexual intercourse and loss of libido/desire. According to statistics, 52% of 40˜70 year old men suffer from varying degrees of SD. And these diseases caused by a variety of biological and psychological factors. In world about 15% of couples are affected by sexual disharmony among these 40 to 50% are because of male factors. Considering the sensitivity of male reproduction system, it is being easily affected by multiple risk factors, such as chronic diseases, environmental contaminants, drug toxicity and unhealthy lifestyle and so on. In the last few years, significant progress have been made toward understanding the various forms of male SD and the possible potential pathological mechanisms. However, for the time being, the exact cause of SD is not fully understood from the literature. What is also significant about there are quite limited treatments in reproductive medicine being directed against these lesions. The purpose of this review is to summarize the current findings of pathogenic factors of SD in clinical or animal studies, to elaborate the underlying mechanisms of these diseases from studies in vivo and in vitro, to analyses the risk factors, and to describe the management strategies traditionally recommended of male sexual dysfunction. The review findings elucidate a systematic strategies for effectively preventing these diseases.

1. Introduction

Male sexuality, a complex physiological process, is an important part of the quality of life. The maintenance of normal sexual function depends on the coordination of human multi-system, involving the coordination of the nervous system, the cardiovascular system, the endocrine system and the reproductive system [1–3]. When the aforementioned system or psychosocial aspects are changed, it will affect the quality of normal sex life. Male sexual dysfunction (SD) is not a single disease. It means the whole process of sexual activity for men, including male sexual arousal, penis erection, penis inserting into vagina, ejaculation, and any obstacle in one link are all called sexual dysfunction [4–5]. Anatomy of penile erection and detumescence can been seen in Fig. 1. In 1992, experts from the National Institutes of Health defined that erectile dysfunction (ED) is that the penis lack of ability to achieve or maintain sufficient rigidity for completing a satisfactory sexual life

Abbreviations: BPA, bisphenol A; CVD, cardiovascular disease; CKD, chronic kidney disease; cGMP, cyclic guanosine monophosphate; DM, diabetes mellitus; ED, ejaculation dysfunction; ET-1, endothelin-1; ER, endoplasmic reticulum; EDC, endocrine-disrupting chemical; eNOS, endothelial nitric oxide synthase; FSH, follicular stimulating hormone; VEGF, vascular endothelial growth factor; STZ, streptozotocin; SD, sexual dysfunction; PCB, polychlorinated biphenyl; PDE-5, phosphodiesterases-5; NO, nitric oxide; LH, luteinizing hormone; HPG, hypothalamic pituitary gonadal; GTP, guanosine triphosphate; GABA, gamma-aminobutyric acid; GnRH, gonadotropin releasing hormone

* Corresponding authors.
E-mail addresses: subinxiaodr@163.com (B.-x. Su), 15769601020@163.com (G.-j. Shi).
[1] Contributed equally.

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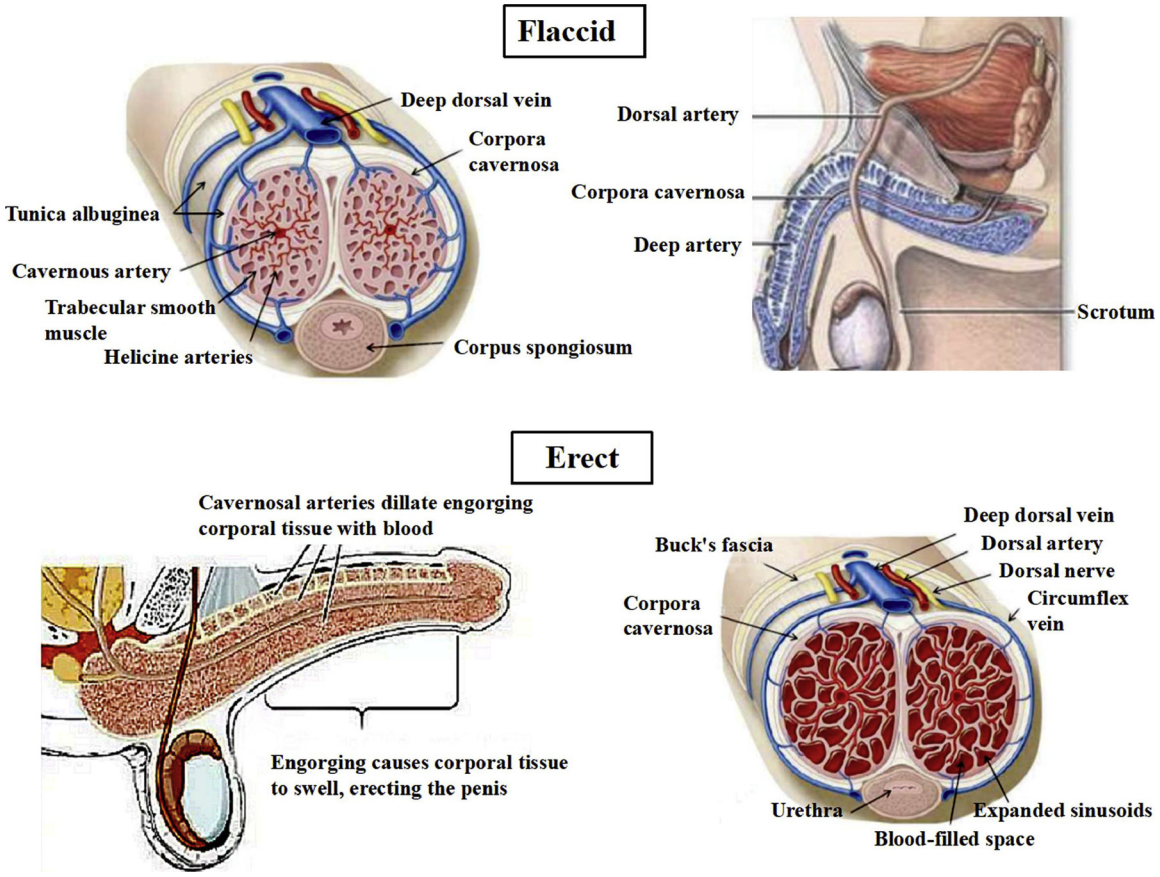

Fig. 1. Anatomy of penile erection and detumescence.

[6]. ED is one of the most prevalent and poorly treated diseases in SD. Disorders of sexual function are common among men of all ages, ethnicities, and cultural backgrounds. The Massachusetts Male Aging Study reported a 52% of 40–70 year old men suffer from varying degrees of SD [7]. In addition, epidemiological evidence suggested that impotence has affected 10 million American men [8]. Although there have been lots of basic studies about SD, the risk factors and pathogeny of this disease is still under exploration.

The male sexual response cycle could be divided into its three component parts: libido (desire), erectile function, sexual activity. All kinds of factors such as psychological factors, surgery and trauma, vascular diseases, neurological factors, etc can cause SD as long as they affect any part of the sexual response cycle. In addition, there are various implicated as risk factors for SD in men such as altered lifestyle, stressful living conditions, various chronic diseases, diverse environmental pollutants and several drug side effects. One estimate placed an overall incidence of drug-associated impotence at 25% in a survey of medical outpatient clinic patients. Many commonly used drugs have been shown to interfere with erection, reduce libido and impair sexual function. Anti-hypertensive drugs have been most commonly related to impotence. Other drugs associated with SD include clofibrate, cimetidine, digoxin, and anti-neoplastics and various hormonal agents. Furthermore, published reports have shown chronic diseases-induced impotence to be a very common finding. Increased evidence suggested that SD could be caused by some disease conditions such as cardiovascular disease [9], hypertension [10], hyperlipidemia [11], diabetes [12], chronic kidney disease [13] or reproductive cancers [14]. With the accelerated pace of life, lifestyle changes and dietary adjustment, the incidence of these chronic diseases is increasing year by year, and their complications of sexual dysfunction are more and more prominent [15]. Moreover, the adversely impact of natural or synthetic environmental agents on male sexual health should not be neglected. More and more literature have been reported, environmental endocrine disruptors, heavy metals and ray radiation have a very serious negative impact on human sexual health. Although male sexual functions were affected by multiple aspects, but currently there are almost total lack of effective treatments in sexual medicine specifically for such lesions. In the 1990s, sildenafil (trade name Viagra) was first approved remedy for impotence, which attracted wide public attention. For the moment, although there are many traditional medicines or herbal drugs have been used by patients with SD with varying degrees of success, herbal products are still anarchically used in many regions and countries, and a great proportion of medicinal plants used traditionally to solve male reproductive disorders have not yet been scientifically evaluated.

In this review, we discussed the risk factors affecting sexual function, elaborated the underlying mechanisms related to male SD via clinical or animal studies, and described the protective effects of medicinal plants or their products. The significance of the review provide a systematic understanding of the occurrence and development of male SD, present our intervention strategies and treatment approach for these diseases, and lay the theoretical foundation for developing the direction of sexual medicine.

2. Pathological mechanisms of male sexual dysfunction

Normal sexual function, a vital part of life required for good health and reproduction, is an intricate process affected by sex hormone level [2,16] and psychogenic [17], neurogenic [18], and hemodynamic factors [19]. Male sexual dysfunction (SD) is a complex physiological process that involves a variety of risk and pathogenic factors; pathological mechanisms that could directly or indirectly affect male SD include endothelial dysfunction (ED) [17], neurogenic factors [20], hormonal pathway [21], and hemodynamic factors [22].

2.1. Endothelial dysfunction and sexual dysfunction

An increasing number of fundamental studies provide evidence that vascular endothelial function plays an important role in penile erection [23]. Nitric oxide (NO) is one of the primary active substances secreted by endothelial cells. NO is a nonadrenergic and noncholinergic vasodilatory neurotransmitter that regulates the vascular wall function [24]. In penile smooth muscles, NO is produced from an endothelial or non-endothelial source. In erection, The NO pathway is activated upon sexual stimulation via the dopamine-oxytocin-nitric-oxide neural pathway [25], leading to erection. Fat-soluble NO directly enters the corpus cavernosum smooth muscle cells, activates guanosine cyclase, and transforms guanosine triphosphate into cyclic guanosine monophosphate (cGMP). The increase in the cGMP concentration contributes to complete diastole of cavernosum smooth muscles in the penis and an obvious rise in the penile blood flow by regulating the K^+ and Ca^{2+} channels on the cell membrane. A large amount of blood is injected into the cavernous sinus, pulling the white membrane and pressing the venous return to achieve rigid erection [26,27,28,29]. In general, the released NO can promote penis erection, regulate hormone secretion of the testis, increase the blood supply of penis, affect sperm quality, participate in spermatogenesis, and affect the male fertility level [26,30]. However, ED is one of the central pathogenic factors that affect various forms of SD and could be due to loss of NO activity. The result of ED can be seen in the ability of the penile vasculature to respond to sexual signals [26]. Researchers. [24] reported that patients with ED had more endothelial damage than those without ED. Koon and other [25] studies found that the number of vascular endothelial stem cells decreased in the blood circulation of patients with ED. These findings indicate that ED may be the first symptom of endothelial injury. Penile erection is a consequence of a series of coordinated and complex events involving neuronal pathways, vascular response, and psychosomatic stimulation. These actions are mediated by the activation of the NO–cGMP dilator pathway [27]. At present, whether early prevention of the NO cascade might supply different or additional benefits for patients with SD caused by ED remains unclear (Fig. 2) [29].

2.2. Hormonal pathway of sexual dysfunction

Endocrine regulation of the male reproductive system maintains normal sexual function by forming a closed loop feedback system. The hypothalamus receives all kinds of information through analysis and integration of the central nervous system and releases gonadotropin–releasing hormones to promote the secretion of follicular stimulating hormone (FSH) and luteinizing hormone (LH) in adenohypophysis. FSH and LH exert negative short-loop feedback to promote the secretion of GnRH, which acts on the gonads to stimulate sexual maturation, gametogenesis, and steroidogenesis. Novel neuropeptides, such as glutamate, gamma-aminobutyric acid (GABA), galanin, dopamine, and kisspeptin, have been suggested to be involved in regulating GnRH secretion. The hypothalamus–pituitary and intratesticular hormones constitute a reproductive regulatory system, which plays a central role in hormonal regulation in male SD. FSH secreted by Sertoli cells plays an important role in testicular development. FSH also maintains the testosterone level in spermatogenic cells, promotes the binding of androgen binding protein (ABP) to testosterone, and regulates the number of spermatogenic cells [31,32]. Investigators also cocultured mouse's spermatocytes and Sertoli cells in vitro and found that adding FSH or testosterone can significantly reduce the apoptosis of spermatogenic cells. In animal studies, the levels of FSH, testosterone T, and LH could be used as the main index for evaluating sexual function. The failure of the pituitary gland to maintain the relative ratio of these endogenous hormones could likely disrupt several processes involved in sexual function to different degrees. Testosterone is an indispensable steroid hormone and the most important androgen for libido and spermatogenesis in males. Normal level of testosterone maintains the male secondary sex characteristics and normal sexual desire, which promotes sperm maturation and protein synthesis, especially in muscles and reproductive organs. Androgen deficiency is a potential cause of many common clinical diseases and may lead to SD, ED, loss of libido, and a decline in reproductive capacity in men. Testosterone replacement therapy may be important in improving sexual thoughts and motivation, number of successful intercourses, number of nocturnal erections, overall sexual satisfaction, and scores of erectile functions in hypogonadal men. However, this treatment does not affect males with normal gonadal development and provides minimal benefits to eugonadal men. The roles of hormones in spermatogenesis and libido must be further investigated to develop methods for improving or treating infertility.

2.3. Hemodynamic factors and sexual dysfunction

Penile erection primarily consists of a series of neurovascular activities and is caused by a net increase in the inflow of blood to the penis [19]. The extent of erection depends on the balance between the amounts of blood perfusing and flowing from the veins [33]. The penis is in a state of relaxation when the arterial perfusion is low and the blood flow is balanced with the venous output [34]. When the arterial infusion of blood increases and the venous outflow volume decreases, the cavernous sinus of the penis becomes swollen and erected because of blood flow. Thus, penis erection is inseparable from artery perfusion, venous blood flow, and fine adjustments between them. Any physiological and pathological factors that cause injury or disturbance to these two aspects can lead to hemodynamic changes in the corpus cavernosum and can directly induce ED [22]. Therefore, the high incidence of SD reported in untreated hypertensive men could be due to alterations in hemodynamics in hypertension. In patients with diabetes, hyperglycemia causes injuries to the normal anatomical structure of the arterial blood vessels, elastic decline in the arterial blood vessels, and contraction and relaxation of the arteries to varying degrees; as such, the arterial blood supply is weakened and filling of the cavernous sinus is slowed down [35]. In patients with cardiovascular diseases, arterial atheromatous lesions may decrease the arterial blood flow, which results in relative ischemia of the arteries, decrease in the oxygen saturation of the cavernous body, dysfunction of the smooth muscles of the cavernous body, and SD acquisition [36]. In summary, several factors may be involved in the SD of hypertensive, diabetic, and angiocardiopathy men. Existing studies do not determine which factors play key roles in SD but aim to reduce penile artery blood flow and obstruct penile erection. Future studies must investigate such factors.

2.4. Neurogenic factors and sexual dysfunction

Normal erectile function requires an intact peripheral autonomic and central nervous system [37]. The roles of monoamine neurotransmitters have been established in animal experiments; meanwhile, human studies have suggested that these transmitters play a key role in mediating sexual desire [38]. The involvement of monoamine pathways in the central nervous system may be the basis for essential hypertension and may cause SD in untreated hypertensive men [39]. This mechanism may explain the higher prevalence of impotence in untreated hypertensive men than in normotensive controls [40]. Furthermore, hypotensive drugs that act by altering neurotransmitters (central and peripheral) may cause SD as a side effect by affecting libido or altering the neural mediation of erectile processes (or both). Interestingly, short-term administration of sympatholytic agents to healthy normotensive volunteers does not interfere with penile blood flow or the ability to become erect upon erotic exposure [41–43]. However, whether this lack of effect is due to short-term exposure to the drugs or whether interference with the ability to obtain penile erection is specific to hypertensive patients remains unclear.

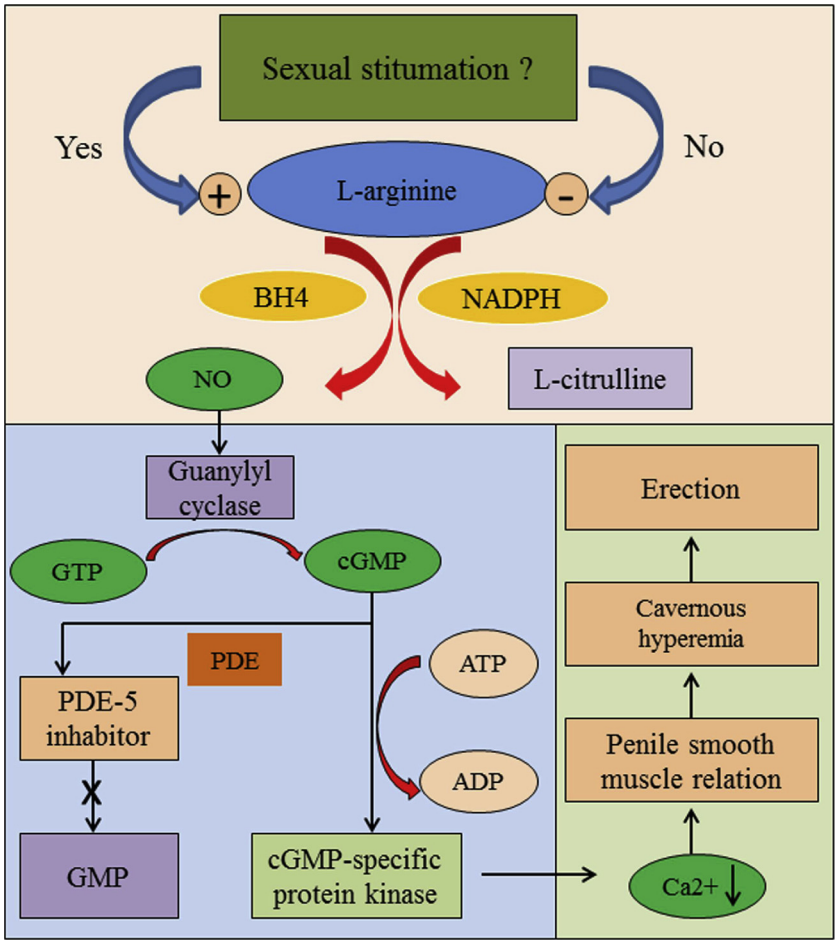

Fig. 2. Physiology of erection.

2.5. Psychogenic factors and sexual dysfunction

Sexual activities supported by healthy sexual psychology can be satisfactory and successful. The normal sexual function must be controlled by healthy psychology. An accidental sexual failure or dissatisfaction may not lead to lasting abnormalities due to normal sexual psychological adjustment. In addition, a healthy sexual psychology is gradually formed by the education, family influence and self-perception of children, adolescents, adolescents and adults in different periods. Patients with performance excessive activity of sympathetic nervous system or anxiety, have an increased cavernous smooth muscle tonicity, and are more likely to lead to penis flaccidity. Major psychotic disturbances can affect erectile function and sexual desire particularly when based upon a chronic organic disease [44]. Normal sexual psychology can relieve their depression and fear, which plays an extremely important role in regulating sexual life of patients. In addition, a functional impotence patient suffers from a burden due to an accidental sexual intercourse failure. Long-term negative psychology will have an inhibitory effect on sexual life, making the penis unable to erect. This is likely to be a non-molecular level mechanism that causes SD in patients. Although organic dysfunction plays a leading role in SD, almost all patients (sexual desire disorder, ED, sensory dysfunction and organic dysfunction) are accompanied by psychological disorders. In this sense, the treatment of SD, whether organic or functional, psychotherapy is very important for patients [45].

3. Risk factors for sexual dysfunction

Numerous epidemiological studies have reported on sexual problems that are prevalent in the society. Sexual complaints, especially ED, occur in 30%–40% men [44]. In most cases, ED was initially considered a psychological disorder but is now regarded as a primary organic complication [43–45]. Medical researchers confirmed that organic ED is caused by hormonal, neurological, or vascular pathologies. Factors that put patients at risk of SD are as follows: 1) adverse environmental factors, such as ionizing radiation, heavy metals, or environmental estrogen over-proof; 2) drugs, including anti-tumor, antihypertensives, and antibiotics; and 3) chronic diseases, such as diabetes and obesity, hypertension, hormonal disturbances, stress, and anxiety (Fig. 3).

3.1. Chronic diseases causing sexual dysfunction

3.1.1. Sexual dysfunction and diabetes and its complications

SD is a common organic complication associated with diabetes mellitus (DM) [31,46] and may include impotence or ejaculation dysfunction (ED), ejaculation disorder (premature or delayed ejaculation), and decrease in libido. In addition, before the 10th Century when Avicenna mentioned that “sexual exhaustion” is a special kind of diabetic complication, people have realized that SD is related to diabetes [47,48,49]. National Health and Nutrition Examination Survey reported that 51.3% of diabetic men suffered from ED [12,50]. ED usually affects diabetic men at an earlier age than nondiabetic men, and the effects of ED increase with the duration of diabetes [51]. Animal studies demonstrated the significant extension of intromission latency and mounting latency and the remarkable decrease in intromission frequency and mounting frequency in streptozotocin (STZ)-induced diabetic mouse models [52]. Diabetes is considered to one of the risk

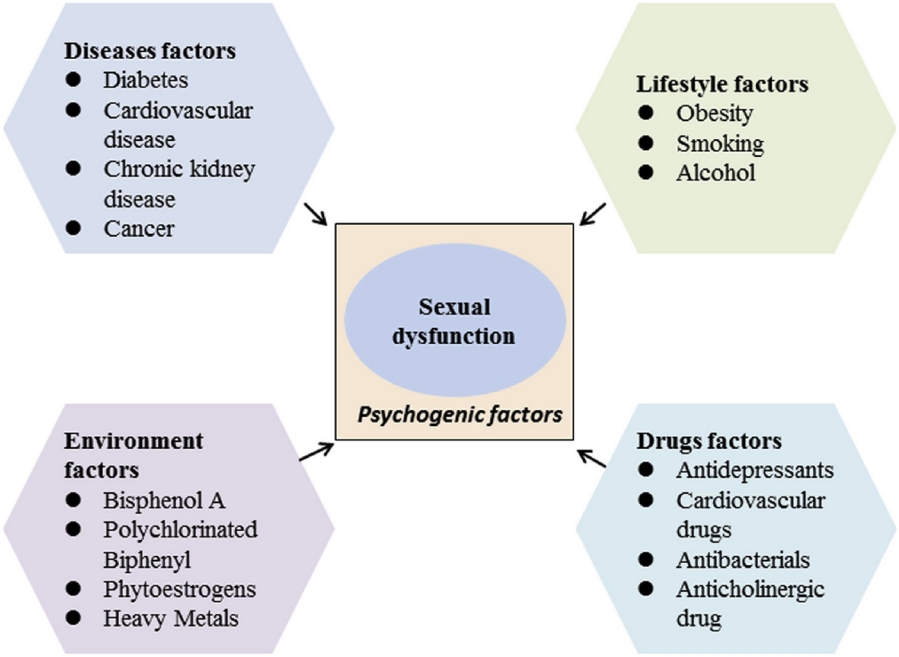

Fig. 3. Factors that determine sexual dysfunction.

factors for developing SD and is also the most difficult complication to treat [53]. The pathophysiology of diabetes-related ED may include vascular insufficiency [54], neuropathy [55], selective degradation of neuronal NO production, reductions in vascular endothelial growth factor (VEGF) expression, increased levels of erythrocyte aldose reeducates, and activation of the RhoA/Rho kinase pathway [56–57]. An explanation is that diabetic neuropathies prevent correct nerve conduction; although the patient may be stimulated, the impulse does not pass to the penis, causing a decrease in the delivery of the smooth muscles of the corpus cavernosum [58]. Moreover, diabetes causes damages to arterioles, leading to alterations in endothelium-dependent relaxation of penile smooth muscles, prevention of the optimal blood flow of the penis, and failure to maintain erection [59]. In patients with types 1 and 2 diabetes, poor glycemic control can damage the blood vessel walls of the penis, impair the NO signaling systems of the corpora cavernosa, reduce the production and increase the consumption of NO; these phenomena eventually lead to abnormal erectile function [60–61]. Therefore, good control of blood sugar and blood pressure in diabetic patients is of great significance in reducing the risks of microvascular and macrovascular complications [62]. Thus far, the involvement of hyperglycemia, a main determinant of vascular diabetic complications, in the pathogenic mechanisms of SD in diabetes remains unclear.

3.1.2. Sexual dysfunction and cardiovascular diseases

Cardiovascular diseases (CVD), including atherosclerosis, hypertension, heart disease, and stroke, are widely considered as multiple risk and predictive factors for SD [63]. A systemic vascular condition affects not only the arteries throughout the body but also the penile and vaginal arteries [64]. Accumulating lines of evidence indicated that SD in asymptomatic men may be a potential marker of undiagnosed cardiovascular diseases. In general, we believe that CVD and SD in males commonly coexist and share many of the same risk factors. We will elaborate the effect of cardiovascular diseases on sexual function.

3.1.2.1. Hypertension. Hypertension has become the most common and prevalent human disease and affects 20%–25% of all adults. Epidemiological survey data showed that approximately 30% of male patients with hypertension experienced ED at different degrees [40]. The degree of erectile impairment is directly related to the duration and severity of hypertension [65]. A recent report showed the lack of difference in the prevalence of ED in hypertensive and prehypertensive men aged 25–40 years old compared with normal controls; as such, the damage caused by hypertension may take several years to show up [66].

3.1.2.2. Stroke. SD is an urgent medical problem for patients who suffered stroke [67]. Many patients and their spouses avoid positive sexual life for fear of recurrent stroke, and interest in sexual behavior is considered taboo for stroke survivors [68]. Stroke makes the patient distressed and depressed and thus has a serious impact on the quality of life. Thompson and others [69] compared the sexual desire of 100 patients before and after stroke and found a more frequent depressed emotional state and significantly decreased sexual desire after stroke. By contrast, in 1999, Park et al. [70] investigated the sexual function, attitudes, and interest of 24 men and 11 women before and after stroke. The results showed no significant changes in sexual desire and interest in women and men [68]. At present, this issue has not been thoroughly investigated. Additional detailed information on basic diseases is essential in future research.

3.1.2.3. Atherosclerosis. The arterial and penile smooth muscle cells of impotent patients suffer from narrowing and atrophy; in this regard, blood cannot be injected normally into the corpus cavernosum of the penis [9,37]. Atherosclerosis is similar to angina or myocardial infarction caused by coronary artery in the elderly. Myocardial ischemia causes myocardial infarction, and penile ischemia leads to impotence. More than 50% of patients with coronary heart diseases suffer from impotence of varying degrees [43]. The ischemia of the cavernous body caused by the arteriosclerosis of the penile arteries is accompanied by anoxia, which causes atrophy of penile tissues, including the muscle and nerve of the blood vessel wall, and results in loss of swelling and drooping during sexual intercourse [71]. Impotence is caused by many factors; in particular, more than 3/4 of impotence cases are caused by organic factors [72]. Although improper drug use, diabetes, hypertension, smoking, drinking, hormone, or balance of chemical medium in the body can cause erectile failure, the most common cause of direct connection is penis blood supply; that

is, cavernous vascular atherosclerosis causes the loss of elasticity of the penis, and the diameter of the cavernous body cannot be fully expanded to accommodate the increased blood supply.

CVDs are risk factors for the occurrence of SD. The severity of heart diseases increases the incidence of SD. In addition, CVD- and SD-related depressive symptoms appear in the rehabilitation process of patients with heart diseases, are characterized by physiological and psychological adaptation, and contribute to decrease in sexual response. Therefore, SD can occur with the development of CVD.

3.1.3. Sexual dysfunction and chronic kidney disease

Male SD is common in patients with chronic kidney disease (CKD), especially end-stage renal disease [13,64]. Scholars have reported the cause of the high incidence of SD in relation to CKD. With the development of CKD, the accumulation of physiological disorders disturbs the activities of other tissues and organs and affects the endocrine system [73]. This complication is most evident in extreme cases, such as dialysis-treated end-stage renal disease [74–76]. The disruption of the HPG axis in men with CKD significantly decreases the sexual function and quality of life. In uremia, cells are affected by chemicals, such as bicarbonates, resulting in electrolyte disturbance, metabolic waste accumulation and reduced secretory function of testosterone in Leydig cells [13,77]. Male patients with uremia are often characterized by lack of erection or erection, low sexual desire, and low ejaculation rate. After dialysis and kidney transplantation, some improvements will be detected, but complete recovery cannot be achieved.

3.1.4. Sexual dysfunction and cancer

Patients with cancer aged less than 44 years account for about 13% of the newly diagnosed cases worldwide [14,78]. Some types of cancer may be associated with temporary or permanent sexual damage or subfecundity. For example, patients with testicular cancer often have poor semen quality upon diagnosis, but most of them achieve good value after treatment; thus, initial semen analysis can predict sperm quality and genetic integrity [79]. The effect of cancer on sexual function could be attributed to the disease itself and its related treatment. Given that a person diagnosed with cancer must be treated immediately [80], damage to sexual function or fertility is usually linked to cancer treatments, such as chemotherapy, radiotherapy, and surgery, which can directly aggravate SD or influence various links associated with SD, such as hormone disorder, nerve damage, and vascular injury of the penis. In addition, SD in cancer patients is not only due to the disease itself but also to the comprehensive result [81] of anemia, anorexia, muscle atrophy, and nerve damage [82]. Moreover, psychological factors, such as fear, despair, and anxiety due to cancer events, greatly affect patients' sexual lives and thus contribute to the incidence of SD.

Different opinions exist about the mechanism of SD or ED caused by various diseases. In general, similar to most diseases, ED can be attributed to the vasculogenic, neurogenic, or endocrinological disorders (Table 1). In addition, SD caused by diseases should be differentiated from other SD types, such as Peyronie's disease, premature ejaculation, and orgasm disorders. However, the precise mechanism is still being investigated.

Table 1
Organic causes of disease related sexual dysfunction.

Vasculogenic causes	Neurogenic causes	Endocrinological causes
• Atherosclerosis Hypertension • Hyperlipidaemia • Diabetes • Increased age • Sinusoidal fibrosis	• Multiple sclerosis • Epilepsy • Parkinson's disease • Alzheimer's disease • A stroke • Spinal cord injury • Pelvic surgery	• Testosterone deficiency syndrome • Hypogonadism • Hyperprolactinaemia

3.2. Other lifestyle factors causing sexual dysfunction

3.2.1. Sexual dysfunction and obesity

Another potential cause of infertility in obese men is the reduced coital frequency associated with obesity [83,84]. In a survey of health professionals, obesity was found to be associated with 1.3-fold relative risk for ED [85]. In men reporting symptoms of ED, overweight or obesity is found in 79% of them [86]. Obesity is also associated with other vascular risk factors rather than obesity itself [83]. Many lifestyle factors with increased risk of cardiovascular diseases and diabetes are also risk factors for ED and have a strong epidemiologic independent link to ED [87]. Limited data suggest that coital frequency may be reduced in obese men [88], and further investigation could contribute to findings of reduced fecund ability among couples, including obese men in studies that did not correct for this factor [89]. If the effect of obesity on coital frequency is confirmed, then further works must determine whether reduced coital frequency is an expression of erectile dysfunction, altered endocrine environment, or psychosocial aspects of obesity.

3.2.2. Sexual dysfunction and smoking

Smoking is an independent risk factor of ED and increases the already high risk of ED in men with atherosclerotic vascular diseases, such as heart disease, diabetes, and hypertension [90]. In an acute animal model, smoking induced vasoconstriction and decreased penile artery inflow and penile venous leakage, resulting in the loss of the normally seen rise in intracavernosal pressure during erection [91]. Similar findings have been reported on the short- and long-term effects of smoking on humans [92]. The short-term effects are believed to be mediated by altering the normal contractile effect of the cavernous smooth muscles and cause acute vasospasm [93]. The long-term effects are less clear but are secondary to the toxic effects of elevated levels of carbon monoxide, increased platelet aggregation, and changes in atherosclerotic vessels. In addition, studies have shown that smoking reduced the arterial blood flow in dogs and led to venous restriction and impaired blood flow to the penis in men who smoke [94]. Therefore, smoking cessation is an important measure for preventing ED.

3.2.3. Sexual dysfunction and alcohol

Intake of a small amount of alcohol leads to elevation of libido or improvement of erectile function by reducing anxiety and inducing vasodilation [15,95]. However, excessive alcohol intake affects all phases of human sexual responses [96]. Chronic alcoholism causes hypogonadism and polyneuropathy, which may affect neural transmission to the penis [97]. Thus, high amounts or long-term intake of alcohol can cause central sedation and transient ED [98]. Many basic and clinical studies have reported that alcohol is implicated in dose-dependent changes in sexual function [99–100]. Chronic alcoholism may lead to decreased testosterone levels, increased estrogen levels, and alcoholic polyneuropathy, which could affect penile nerves [100]. In a group of patients subjected to hospitalized alcohol abstinence, 75% have reported SD in the first 6 months and 66% of them remained sexually impaired up to 9 months after the treatment [101]. Approximately 50% of the respondents believed that SD was directly related to the amount of alcohol consumed [102].

3.3. Environment factors causing sexual dysfunction

Occupational or long-term exposure to certain toxins and chemicals, such as herbicides and pesticides, may affect sexual function and reduce sexual desire by changing the hormone system. Estrogenic and hormone destructive chemicals, such as bisphenol A [103], phthalates, and organochlorine, are particularly potential problems [104]. Long-term exposure to heavy metals [105], such as lead, cadmium, or arsenic, may affect sexual function. However, no strong evidence is available to support the serious harmful effects of exposure to these chemicals on sexual function of men.

3.3.1. Bisphenol A and sexual dysfunction

Synthetic compounds may exert endocrine disrupting characteristics. Bisphenol A (BPA) is an organic synthetic compound with hormone-like properties [106]. BPA is a colorless solid and is used in the manufacture of certain plastics and epoxy resins as well as in water bottles, sports equipment, water pipe lining, and coating of various food and beverages [107,108]. A research on Chinese factory workers indicated that those exposed to BPA had higher risk of SD than non-contact workers [109]. Bodnar et al. found that high BPA levels in urine and blood can be used as a sign of decline in male sexual function [103]. Another study evaluated the corpus cavernosum tissues of rabbit after administration of BPA; the results indicate that BPA might affect erectile function through histological changes in the corpus cavernosum [110]. Moreover, analysis of an animal model revealed that the combination of BPA and high-fat diet could enhance testicular dysfunction [63]. However, these results have yet to be reproduced in human studies due to the increased acceptance of BPA as an endocrine-disrupting chemical. However, the consumption of BPA should be prudent.

3.3.2. Polychlorinated biphenyl and sexual dysfunction

Another synthetic compound with endocrine disrupting properties is polychlorinated biphenyl (PCB) [111]. Studies on rodents showed that the male offspring of mothers given with PCBs during pregnancy developed smaller testicles, epididymis, and seminal vesicles and lower sperm counts [112]. Nakayama et al. demonstrated that PCB exposure may negatively affect testosterone levels in adolescent male humans [113]. However, this chemical may not cause clinical symptoms of hypogonadism in young adults. A recent study that compared organochlorine levels between men with ED and controls found that these chemicals did not increase the risk of ED [114]. Another study reported no difference in semen quality between fertile farrow people with high and low blood concentrations of PCB homologs [115]. However, men with higher PCB concentrations possessed higher FSH levels. These studies suggest that PCBs exert endocrine-disrupting properties; however, whether these chemicals are clinically significant in humans remain unknown.

3.3.3. Phytoestrogens and sexual dysfunction

Endocrine disruptors, which are rich in phytoestrogens and a source of heterologous estrogens in human diet, are found in food, including beans, fruits, and vegetables. Among phytoestrogens, isoflavones, lignans, and coumarins are the most studied and have the greatest effect on human physiology. Pan et al. found that exposure of juvenile rats to large doses of daidzein impaired erectile function and decreased the plasma testosterone levels. Another study showed that daidzein-treated rats possessed increased amounts of collagen, smooth muscles, and elastic fibers in their corpus cavernosum, suggesting the presence of vasculogenic ED. Many animal studies support the possibility that phytoestrogen can alter human reproductive and sexual health through its endocrine-disrupting characteristics. However, the discovery of these disruptors in animals remains challenging because of excessive confounding variables. High levels of isoflavones were found in blood and urine after eating soy; however, whether high levels of phytoestrogens in blood can affect the hormone environment or lead to adverse consequences. A case report by Martinez et al. described a man with long-term ingestion of high levels of soy milk who developed gynecomastia and possessed estrogen levels four times the normal value. Nevertheless, high phytoestrogen concentrations may lead to adverse hormonal effects; as such, moderation of dietary intake is important to avoid the disruption of the HPG axis.

3.3.4. Heavy metals and sexual dysfunction

Heavy metals, which have high atomic weights, can function as endocrine disruptors [116] and are found to be highly concentrated on the earth because of human manipulation [3,117]. Lead is one of the most abundant heavy metals in the earth's crust and has many industrial uses. Lead was historically used in paints, pipelines, and fuels; however, developed countries have aimed to decrease the use of lead because long-term exposure to this metal is toxic. Multiple studies also linked lead exposure to ED. Gonulalan and colleagues compared erectile function between men with chronic lead intoxication and non-exposed male controls; the group exposed to lead had higher incidence of ED than the controls [118]. Anis and colleagues extrapolated on this study design and compared blood lead level between men with severe ED and healthy controls [119]. Scholars found that lead levels were significantly high in men with erectile problems [120] and that all affected men had severe ED. These results indicate that the increase in the lead level can directly affect the corpus cavernosum and eventually the function of its smooth muscles. On a molecular level, lead acetate can negatively regulate the effect of NO on guanylate cyclase and potassium channels, resulting in ED [26]. Lead suppresses testicular steroid production by inhibiting the 3β and 17β hydroxyl steroid dehydrogenase pathways, thereby decreasing the count, viability, and vitality of sperm.

3.4. Drugs causing sexual dysfunction

Many commonly used drugs can interfere with male sexual function either by decreasing libido, interfering with erectile function, or causing absent seminal emission or retrograde ejaculation. The effects of drugs on sexual function may be difficult to distinguish from those of organic disease, anxiety, and depression; as such, physicians should be aware of the drugs most commonly associated with SD [121]. Moreover, agents with sympatholytic activity can inhibit ejaculation and prevent bladder neck closure, thereby allowing retrograde ejaculation. Drugs blocking cholinergic transmission will affect the parasympathetic branch of the autonomic nervous system and may lead to inadequate smooth muscle relaxation within the corpora cavernosa; this phenomenon could prevent the normal cascade of events and increase the arterial blood flow with simultaneous venous compression. Centrally acting medications may cause sedation/depression and reduced libido. Hormonal changes can cause impotence and hypogonadism by increasing the levels of circulating prolactin. Agents, such as spironolactone, are believed to act as antiandrogens. However, differentiating the effects of a particular drug on sexual function from the effects of the disease that led the patient to use the drug remains difficult. Patients often take multiple medications concurrently, causing complex interactions, which add to the difficulty in determining the adverse effect profile of a particular drug. In the next section, we present a review of commonly used drugs that could cause impotence (Table 2).

4. Strategies for managing sexual dysfunction

The pharmacological treatment incorporating the psychological and sociological input is essential. The Sexual Tipping Point™ provides a viable model for conceptualizing etiology and a biopsychosocial combination therapy for all SD. Sexual pharmaceuticals and coaching can be integrated to address the psychological, organic, and cultural issues for men with ED [122]. In addition, multiple strategies involving dose reduction and drug switching have been attempted to reverse drug-induced SD. As the standard of care for men, administering phosphodiesterase type 5 inhibitor prior to intercourse can improve erection in about 70% of male hypertensive patients. Scholars have established the cause of hyperprolactinemia in patients taking antipsychotics and recommend reduction in the drug dose or use of prolactin-sparing drugs. Nevertheless, specific concerns of the patients should be determined and addressed [4]. The proposed solutions for gabapentin-induced anorgasmia include reducing the drug dose, administering a regular dose during planned sexual intercourse until anorgasmia no longer occurs, use of alternative drugs, and co-administration of other drugs. However, phosphodiesterase type 5 inhibitors are contraindicated in men who use nitrates and should be carefully used in patients taking alpha

Table 2
The pharmacist of drugs and other substances involved in erectile dysfunction.

Drug class	Decreased desire	Decreased arousal	Orgasm or ejaculatory difficulties
Antidepressants	amitriptyline clomipramine fluoxetine imipramine paroxetine phenelzine sertraline	amitriptyline citalopram clomipramine doxepin fluoxetine imipramine nortriptyline paroxetine phenelzine sertraline tranylcypromine	citalopram clomipramine doxepin escitalopram fluoxetine* fluvoxamine imipramine nortriptyline paroxetine* sertraline* tranylcypromine venlafaxine
Other psychotropic drugs	alprazolam chlorpromazine fluphenazine haloperidol lithium risperidone	chlorpromazine fluphenazine lithium risperidone	alprazolam fluphenazine haloperidol risperidone
Cardiovascular drugs	clonidine digoxin hydrochlorothiazide methyldopa spironolactone	beta blockers clonidine digoxin hydrochlorothiazide methyldopa perhexilene spironolactone	
Antibacterials	Ketoconazole	Metronidazole	
Cardiac glycosides	Digitalis Digoxin		
Antipyretic analgesics	Indometacin Phenylbutazone Phenacetin		
Anticholinergic drug	Atropina Anisodamine Probanthine		Trihexylphenidyl
Antihistamine			Cimetidine Ranitidine
Antineoplastic drugs	——	——	——
Other drugs	cimetidine	antihistamines cimetidine cyproterone disulfiram gonadotrophin-releasing hormone agonists propantheline pseudoephedrine	naproxen

blockers because postural hypotension may be a problem. Therefore, effective prevention of SD caused by various risk factors is important in clinical practice [122].

For all patients, Correct understanding and changing the modifiable risk factors of potential risk factors is the first step in prevention and treatment of these diseases, but it may not be sufficient to completely reverse ED. The risk factors that could be potentially changed include psychosocial factors, lifestyle, iatrogenic causes, sexual technology, and information-related factors. Most patients with ED need to be treated. ED can be managed using herbal medicines because of their long history of utilization; moreover, natural products have gained increasing interest for maintaining good health worldwide. To understand the value and role of traditional medical knowledge in health care, further studies must be conducted on the efficacy and safety of herbal medicine for treatment of ED. Developing natural supplements from medicinal plants is being intensified probably due to their significant potency, reduced side effects, ready availability, and low cost. Therefore, medicinal plants with aphrodisiac potential must be further explored. In this review, all herbal plants used exhibited significant pharmacological activity. Natural herbal plants are a source of medicine because of their beneficial therapeutic properties, rich resources, multi-targeted efficacy, and low toxicity and drastic side-effect. The general public recognized the value of natural herbal plants as a source of new or complimentary medicinal products. Modern scientific studies on experimental animals have reported that a large number of herbal drugs can be used to control fertilization. Various phytoconstituents, such as alkaloids, flavonoids, tannins, xanthones, triterpenes, and quinones, regulate reproductive activity. Herbal plants are typically used to manage SD primarily because of their vascular protection or oxygen radical scavenging through various mechanisms [32] (Table 3).

5. Future directions

Issues in sexual desire and activity are widespread, regardless of economic status, gender, and age. The prevalence of ED and other SDs considerably increases because of the rapidly aging population. SD may cause serious distress for patients and requires attention and care. Our understanding of the pathophysiology of ED and SD has been driven by the effectiveness of therapies that affect one or more of the pathophysiological pathways. However, whether PDE-5 inhibitors benefit millions of men with ED remains unclear. As we further investigate the central and peripheral effects of hormones on the sexual response cycle,

Table 3
Medicinal plants and plant-derived products used as aphrodisiac and for the management and treatment of male sexual dysfunction.

Plant	Plant family	Part used	Extract	Dose/model/ duration	Effects observed on sexual dysfunction	References
Anacyclus pyrethrum	Asteraceae	roots	Ethanol solution extract	50, 100 and 150 mg/kg for 28 days	The extract had a marked influence on body and accessory sexual organ weights of the rats, and they were more receptive and oriented towards female rats and increased pre-copulatory activates such as licking and sniffing. The penile erection index was significantly increased with reduction in mount latency and intromission latency period, 4-fold increase in mount and 3-fold increase in intromission frequency	[123]
Anethum graveolens L	Apiaceae	————	————	50 mg/kg BW for 1, 7 days	The extracts on the mounting frequency, histology of tests and epididymis, and sperm physiology. It significantly increased the mounting frequency, and the rat tests showed high levels of phosphorylated proteins. In histological analyses, AG extract did not affect the sperm concentration, acrosome reaction and histological structures of tests and epididymis.	[124]
Alpinia calcarata Roscoe	Zingiberaceae	————	Hot water extract	150, 250 and 500 mg/kg	The extracts possessed strong aphrodisiac action as evident by significant reduction in mounting and intromitting latencies; it markedly prolonged the latency for ejaculation, nonimpairment in libido, sexual arousability, sexual vigour and sexual performance or penile erectile ability. The authors concluded that A. calcarata rhizomes possess a strong and safe oral aphrodisiac activity	[125]
Arctum lappa L	Asteraceae	roots	————	600 and 1200 mg/kg body weight	The extracts significantly increased the MF, IF and EF, reduced ML IL and, prolonged PEI and EL. In addition, the extract also significantly increased the frequencies of all components of penile reflexes as well as serum testosterone levels. The authors concluded that aphrodisiac eff ;ects of the plant extract may be related to the presence of flavonoids, saponins, lignans and alkaloids, acting via a multitude of central and peripheral mechanisms.	[126]
Asparagus adscendens Roxb	Asparagaceae	roots	Ethanol solution extract	100, 200 and 300 mg/kg body weight for 30 days	It was found that the extract significantly increased body weight, testes weight, testicular tubular diameter and number of round/elongated spermatids, MF, IF and EL. The authors concluded that A. adscendens possessed aphrodisiac activity and could be used for the treatment of sexual disorders as evidenced by the results showing increased anabolic, reproductive and sexual activities.	[127]
Chione venosa Sw.	Rubiaceae	stem bark and the roots	Dichloromethane and methanolic-aqueous extracts	————	Watcho et al. (2012) found that β-sitosterol obtained from M. whitei significantly increased the mount frequency, penile erection and ejaculation latency in experimental male rats. However, a further study based on pre-clinical and clinical findings for the aphrodisiac potential of other identified phyto-constituents is required to scientifically validate the traditional claim.	[128]
Chlorophytum borivilianum L	Liliaceae	dried root	Aqueous extract	125 and 250 mg/kg, after day 14 and 60	Similarly, at the higher dose (250 mg/kg), all parameters of sexual behavior were enhanced but showed a saturation effect, the sperm count increased significantly. The authors concluded that roots of CB can be useful in the treatment of certain forms of sexual inadequacies, such as premature ejaculation and oligospermia	[129]
Cinnamomum cassia	Lauraceae	bark	Methanol extract	————	Cinnamomum cassia extract significantly increased sexual function. The extract also increased smooth muscle level and decreased collagen level in rat penile tissue. The authors concluded their studies by scientifically validating the C. cassia effect on increasing sexual function.	[130]
Corchorus depressus Linn.	Tiliaceae	————	Methanol extract	25 mg/ml in vitro and 400 mg/kg in vivo	The chloroform fraction of methanolic extract significantly reduced ML, IL, PEI and III and significantly increased MF, IF and EL, serum testosterone levels, erections, quick flips, long flips and total reflex	[131]
Cydonia oblonga Miller (quince)	Rosaceae	————	Hydroalcoholic extract	500 and 800 mg/kg body weight for 28 days.	They observed sexual parameters such as mounting frequency, assessment of mating performance and orientation activities towards females, towards the environment and towards self. It was found that the extract significantly increased the MF, mating performance and attraction to females in comparison with non-treated rats	[132]
Cyperus esculentus L	Cyperaceae	————	————	1 and 2 g kg-1 day-1 for 30 days	The treatment reduced mount and intromission latencies in both groups, while intromission frequency and ratio were increased in moderately active rats and serum testosterone levels increased significantly in both groups. The authors concluded that C. esculentus significantly stimulated sexual motivation and improved the sexual performance of male rats	[133]
Dracaena arborea Wild	Dracaenaceae	dried root barks	Aqueous and ethanolic extracts	(100 and 500 mg/kg for 28d	The authors found that both extracts significantly increased MF and IF while ML, IL and PEI decreased. They concluded that D. arborea possesses aphrodisiac potential and that	[134]

(*continued on next page*)

Table 3 (*continued*)

Plant	Plant family	Part used	Extract	Dose/model/ duration	Effects observed on sexual dysfunction	References
					this effect might be due to antioxidant and androgenic properties of phenols, flavonoids, saponins and sterols	
Fadogia agrestis	Rubiaceae	————	Aqueous extract	50 and 100 mg/kg for 28 days	All the doses resulted in significant increase in mount frequency and intromission frequency and significantly prolonged the ejaculatory latency, while mount and intromission latency was reduced. There was also a significant increase in serum testosterone concentrations in all the groups in a manner suggestive of dose dependence.	[135]
Garcinia kola Heckel	Clusiaceae	————	70% ethanolic extract	100, 200 and 400 mg/ kg daily for 56 days	It was found that G. kola significantly increased the components of libido, erection, ejaculation, testicular weights and sperm count and increased serum testosterone in treated rats. The authors concluded that G. kola seed extract possesses potent aphrodisiac activity in male albino rats with resultant increase in sperm count and testosterone levels.	[136]
Humulus lupulus L.	Cannabaceae	————		25 and 50 mg/kg	The author investigated the influence of H. lupulus extract on sexual behaviour of both naïve and sexually potent male rats. They observed and reported that in naïve rats the acute administration of H. lupulus extract significantly reduced the percentage of mounting and ejaculating animals.	[137]
Lecaniodiscus cupanioides	Sapindaceae	root	Aqueous extract	————	It was found that alkaloids, anthraquinones, phenolics, saponins and tannins were present in the extract. Lecaniodiscus cupanioides significantly reversed the paroxetne-mediated alterations in MF, IF, EF, ML, IL, EL, PEI, and testosterone, folliclestmulatng hormone and luteinising hormone concentrations dose dependently.	[138]
Monsonia angustfolia	Geraniaceae	————	Crude aqueous extracts	3, 30 and 300 mg/kg	It was found that the extract different dose significantly increased the mount frequency, intromission frequency, ejaculation frequency, ejaculation latency and serum hormone concentrations. The authors concluded that administration of 300 mg/kg bw of the aqueous extract produced the best effects in all parameters	[139]
M. frutescens and M. grandiflora	Asteraceae	————	Aqueous crude extracts o	————	They reported that systemic administration of the aqueous crude extracts of Montana plants elicited significant increase in the ejaculatory capacity of spinal male rats with very robust ejaculatory motor patterns that included the expression of tonic penile erections and penile movements and the potent expulsion of urethral contents. Montanoa frutescens and M. grandiflora increased the ejaculatory potency with aphrodisiac activity similar to M. tomentosa.	[140]
Microdesmis keayana J.Léonard	Pandaceae	————	Aqueous extract	aqueous extract 150 mg/kg and pure alkaloids (3 mg/kg)	The author investigated the aphrodisiac prop- erties of M. keayana J. Léonard root extract and major isolated alka- loids by observing the sexual behaviour of male rats. They observed and reported that aqueous extract (150 mg/kg body weight) and pure alkaloids (3 mg/kg body weight) stimulate sexual parameters in rats' sexual behaviour.	[141]
Montanoa tomentosa	Asteraceae	————	Aqueous crude extract	38, 75 and 150 mg/kg	Carro-Juárez et al. (2014) found that the cihuapatli extract acts directly at the male rat spinal system in charge of the expression of the ejaculatory motor patterns; it is suggested that the aqueous crude extract exerts its aphrodisiac properties by increasing sexual potency acting as an oxytocic agent	[142]
Moringa oleifera Lam.	Moringaceae	————	Hydroethanolic extract	————	During 7-day treatment, the extract improved sexual performance in stress-exposed rats by decreasing IL and increasing IF, suppressing PDE-5 activity, decreasing serum cortcosterone level, but increasing serum testosterone and numbers of interstate Leydig cells and spermatozoa. The authors concluded that the increased sexual performance during the intromission phase may be due to the suppression of MAO-B and PDE-5 actives and increased testosterone; possibly, this is due to the effect of antioxidant phytoconsttuents of the extract.	[143]
Turnera diffusa Wild	Turneraceae	————	Aqueous extract	10 and 80 mg/kg	Turnera diffusa significantly increased the percentage of males achieving one ejaculatory series and resuming a second one and also reduced the PEI. They concluded that pro-sexual effect of the aqueous extract of T. diffusa in rats involves the participation of NO pathway, mainlyat central level.	[144]

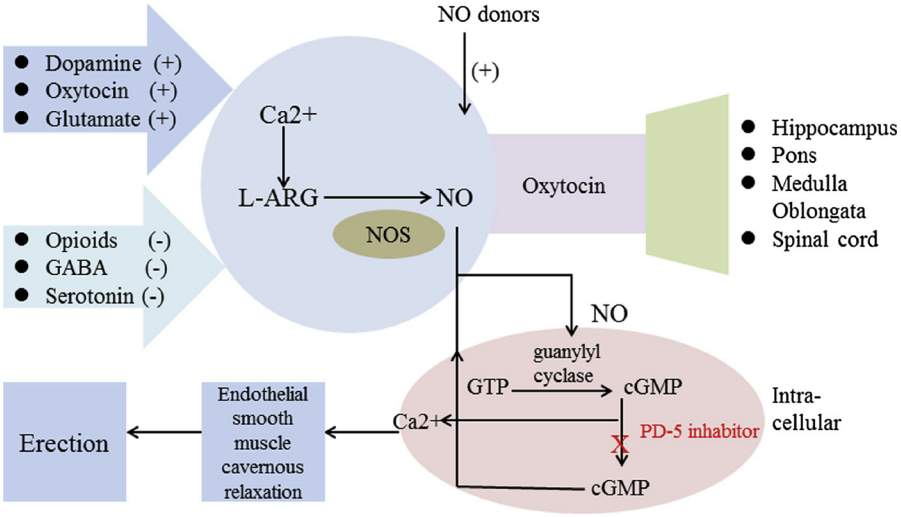

Fig. 4. The role of dopamine-oxytocin-nitric oxide pathway in the erection function.

our understanding of hormonal and dopamine-oxytocin-nitric oxide pathways related to sexual function also improves [25] as seen in Fig. 4. Thus far, besides sildenafil and its related drugs, no other medicine exerts ideal therapeutic effects. Hence, the mechanisms discussed above are not the sole factor affecting SD. Thus, future works must focus on specific molecular targets of male SD that may affect spermatogenesis, testicular cell differentiation, sex maturation, and sperm production. Ongoing research on the alternative pathways of enhancing male sexual responses, including centrally acting agents, could contribute to achieve further breakthrough in treatment barriers.

Competing interests

The authors declare that there are no conflicts of interest.

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