Review Article

iMedPub Journals
www.imedpub.com

Translational Biomedicine
ISSN 2172-0479

2021
Vol.12 No. 10:9903

A Review on Epidemiology, Risk Factors, Molecular Etiology and Management of Various Forms of Sexual Dysfunction - Special Focus on Erectile Dysfunction and Libido

Srividhya Sundararaman[1*], Harish Mohan[1], CN Ramchand[2]

[1] Sipwise Beverages Pvt Ltd, Vadodara, India; [2] Saksin Lifesciences Pvt Ltd, Taramani, Chennai, India

[*]**Correspondence to:** Srividhya Sundararaman, Sipwise Beverages Pvt Ltd, Vadodara, India; Tel No: 8754505956; E-mail: drsrividhya.s@sipwisebeverages.com

Received Date: August 03, 2021; **Accepted Date:** October 19, 2021; **Published Date:** October 29, 2021

Citation: Sundararaman S, Mohan H, Ramchand CN (2021) A Review on Epidemiology, Risk Factors, Molecular Etiology and Management of Various Forms of Sexual Dysfunction - Special Focus on Erectile Dysfunction and Libido. Int Transl Biomed Vol: 12 No: 10

Abstract

Sexual dysfunction in both men and women are caused by some common factors such as smoking, alcoholism, psychological stress, unhealthy lifestyle and other medical conditions like diabetes, organ failure etc. Similar to the shared causes for the condition, a subset of molecular pathways and etiology behind the condition are also overlapping between the sexes. Studies have demonstrated that ED is increasingly prevalent with age: approximately 40% of men are affected at age 40 and nearly 70% of men are affected at age 70. Pathways like NO/cGMP signalling, RhoA/ROK mediated calcium sensitizing pathways, testosterone and estrogen mediated gene regulation, neurotransmitter balance etc. have been shown to be the driving forces behind the smooth muscle tone, libido, penile erection and ejaculation. Currently, the only available treatment modality for ED is oral administration of PDE5 (Phosphodiesterase 5) inhibitors and hormone therapy. In spite of this, there is a constant need for a much simpler and cheaper method that can prevent or treat various types of sexual dysfunctions with none or lesser side effects. These reasons have altogether carved a niche for cheaper and safer alternatives to mainstream medication.

In this background, this review vividly elucidates the risk factors, molecular etiology, role of key players like hormones and signalling pathways, current treatment modalities and upcoming surge of Nutraceuticals in the management of sexual disorders; majorly focussing on erectile dysfunction (ED), molecular pathways and psychological drive behind libido. The review also touches upon the list of aphrodisiacs and their modes of action in the context of prevention and treatment of sexual dysfunction in both sexes.

Keywords: Libido; erectile dysfunction; corpus cavernosum; smooth muscle; NO-cGMP signaling; aphrodisiacs

Introduction

Maintenance of a healthy sexual life is very indispensable considering the poor quality of food and ballooning environmental threats in today's world. In fact, it is unsurprising to mention that it has almost become a challenge to stay healthy both generally and sexually. In this context, it has become a matter of grave concern to understand the etiology, risk factors and mechanisms of how a myriad of chemicals pose a potential threat to human fertility, given the dangerous fact that we are exposed to a plethora of deadly chemicals in our domestic lives. However this does not rule out the other factors responsible for increasing infertility such as lifestyle changes, career and relationship related stress, side effects cause by medications, accumulated genetic mutations, excess drinking and smoking, excessive use of pesticides etc. Besides these general causes, there are more specific health related issues that predispose the body to sexual dysfunctions; to mention a few, diabetes mellitus, cardiovascular diseases, hypertension, stroke, atherosclerosis, chronic kidney disease, psychiatric conditions etc.

Nearly 43% of women and 31% of men are affected by sexual dysfunctions. Population based studies state that Hypoactive sexual desire disorder (HSDD) is prevalent in 30% women and 15% men. Sexual arousal disorders were identified in nearly 10-15% of men and women. Another community based study identified orgasmal disorder in 10-15% individuals. The most common problem in men was found to be premature ejaculation in 30%. Sexual arousal disorder was found to be more common in women 10-15% than men (less than 5%) [1]. A study report involving 27,839 men from 8 countries identified that erectile dysfunction (ED) is prevalent in nearly 16% men and only 58% of them seek medical advice[2]. Another study conducted in USA identified ED in 18.4% men [3]. Sexual dysfunction is a silent struggle and is mostly under-reported partially owing to the social stigma associated with the concept and also due to difficulty with understanding and defining the condition. Especially with woman, it is majorly not noticed or even if noticed, not given much importance and hence its etiology is poorly understood.

Among various other models proposed for sexual response cycle, the widely accepted DEOR model divides it into 4 phases namely desire (libido), excitation (arousal), orgasm and resolution [4]. These phases are generally experienced by both men and women, however the duration of each phase are very subjective and vary with sexes. Disability with one or more of these phases leads to dissatisfaction and is recognised as sexual

disorder or inability. Proper diagnosis, counselling and/or medications will have to be decided and given cautiously in a very personalized manner to avoid further complications.

Unlike many other diseases, sexual problems are multifaceted and encompass various subsets of conditions within it and are not successfully treated in all cases due to their confounding nature. Male sexual problem can arise from problems with desire, arousal, orgasm or due to pain. Erectile dysfunction is the most commonly prevalent and the most researched sexual disorder in men. Studies done a decade ago indicate that erectile dysfunction affected 18 million men just in the US and is often associated with systemic diseases, educational background, lack of physical activity etc.[3]. Ejaculatory disorders like premature ejaculation, delayed ejaculation, retrograde ejaculation, painful ejaculation, anejaculation etc. also are reported with rare to common prevalence depending on the demography. In contrast to the prodigious amount of knowledge and data about male sexual problems especially, erectile dysfunction, there is a dearth of information on the female sexual dysfunctions majorly owing to the stigma attached with the topic and lack of awareness regarding personal identification of the problem. Some of the most prevalent FSD include vaginismus (coital disorder), anorgasmia (orgasmal disorder), dyspareunia etc. (painful intercourse). Hypoactive sexual desire disorder (HSDD) and sexual aversion disorders (SAD) albeit their crucial significance are very less frequently reported and are poorly studied both clinically and empirically both in men and women.

Sexual wellbeing is driven by a plethora of molecular pathways that play in harmony and in a well-orchestrated manner with numerous feedback loops. Psychological stimulation in one of the sensory modalities like gland penis, psychic impulses, auditory, visual or other olfactory cues like smell, touch etc. is the first trigger in this context. This activates the autonomic nerve system involving both sympathetic and parasympathetic nerves along the central and peripheral nervous system [5]. This process is concomitantly enabled by different subsets of gonadal hormones and genital receptors. Extensive optogenic studies have demonstrated the involvement of medial preoptic area (mPOA) in sexual behaviour. This is a sexually and anatomically dimorphic region in hypothalamus and mediates sexual behaviour in both male and female [6]. Microinjection of dopamine agonist and antagonist into mPOA have proven how dopamine acts as 'engine' for erection [7]. Similar sexual stimulatory effects have been reported with L-Glutamate [8]. There are studies that demonstrated a strong positive correlation between Nitric oxide and dopamine release in mPOA [9]. In contrast to dopamine, serotonin is generally considered to have an inhibitory role in sexual behaviour, although depending on the receptor (5-HT) subtype [10]. However the mechanism by which various intracellular messengers and neurotransmitters in MPOA neurons regulate the excitatory and inhibitory effects of dopamine, NO, glutamate, GABA, serotonin etc. is yet to be fully explored. NO-cGMP signalling is another very inevitable biochemical pathway that plays the most important role of smooth muscle relaxation in both male and female. Close interplay between NO signalling and sexual performance have been well established in animals and humans. Nitric oxide is a potent relaxant of corpus tissues (corpus spongiosum and corpus cavernosum) that plays a major role in penile erection. Increase in levels of NO triggers the release of cGMP and eventually increases blood flow to the male or female sex organs through phosphorylation of various membrane kinases and regulating intracellular calcium levels[11]. A lion's share of work is performed by steroid hormones like estrogen, testosterone, progesterone and gonadotropins like follicle stimulating hormone (FSH), luteinizing hormone (LH).

Treatment modality for sexual dysfunction is highly subjective and solely depends on the specificity of the problem and cannot have a generalised approach. Female sexual dysfunctions are often treated with hormone therapy with estrogen or testosterone depending on the need, however with proper labelling regarding reported side effects as advised by FDA. Osphena® (ospemifene) is the first and only FDA-approved drug to treat vaginal dryness and coital pain. Addyi® (flibanserin) is prescribed as anti-depressant for treating hypoactive sexual desire disorder (HSDD). Increased success rates, cost-effectiveness and popularity has led to profuse use of Phosphodiesterase (PDE5) inhibitors like viagra® (sildenafil), Cialis® (tadalafil), Levitra® (vardenafil), and Stendra® (avanafil). Other common therapy specifically for erectile dysfunction include inflatable and non-inflatable penile prosthesis, ICT, stem cell therapy, intraurethral suppository etc. Low- intensity shockwave therapy (lithotripsy), platelet-rich plasma injection are emerging as new therapeutic methods to treat ED [12].

Apart from the mainstream medications and treatment modalities, 'dietary supplements' (DS) have always left their footprints for prevention and better management of disease. DS or Nutraceuticals do not fall under the regulatory jurisdiction of the FDA, leaving us with poor insight into their mode of action, efficacy and safety. Albeit this lacuna in their credibility and knowledge, we still use supplements and herbal products for assorted health conditions and especially for sexual wellness on the basis of their traditional knowledge and the results obtained from clinical studies. There are hundreds of vasodilating agents identified from plants, majority of which fall under the broad category of alkaloids, flavonoids and terpenoids and most of them were found to act through NO/cGMP pathway [13]. For instance, endothelial nitric oxide synthase (eNOS) expression was found to be upregulated with phytochemicals like Betulinic acid, a pentacyclic triterpene isolated from Zizyphi spinosi[14], flavonoids like luteolin and cynaroside from artichoke Cynara scolymus[15], Ursolic acid, a pentacyclic triterpene from Salvia miltiorrhiza [16] etc.

Numerous clinical trials have proven the fact that various phytochemicals exhibit androgenic activities; to mention a few,

- 'Protodioscin' from Tribulus terrestris increase serum testosterone by readily converting to DHEA or releasing DHEA from serum proteins probably [17].
- Plant sapogenin called 'Diosgenin' from fenugreek increase serum testosterone directly or indirectly by releasing testosterone from serum globulins [18].
- Eurypeptides from Tongkat ali increase DHEA levels probably by activating Cyp17 enzyme [19].

- Ginsenosides from Korean ginseng increase serum testosterone probably via stimulation of leutenizing hormone [20]. There are a number of phytochemicals like flavonoids, stilbenes, pterocarpans, coumestans etc. that are well identified as phytoestrogens as they harbour the phenolic rings that resemble estrogen and thus bind to estrogen receptors and participate in sexual processes culminating in enhanced libido response[21].

Herbal aphrodisiacs fall under the broad category of 'Dietary supplements' according to FDA and the market keeps increasing throughout the world in spite of the pitfalls associated with them like lack of various facts like unified regulations, definition, pragmatic approach etc. They are not approved by FDA and hence do not undergo the scientific scrutiny as other drugs in the market. This is majorly due to the lack of rational approach to prove the mode of action, pharmacokinetics and toxicity of these compounds.

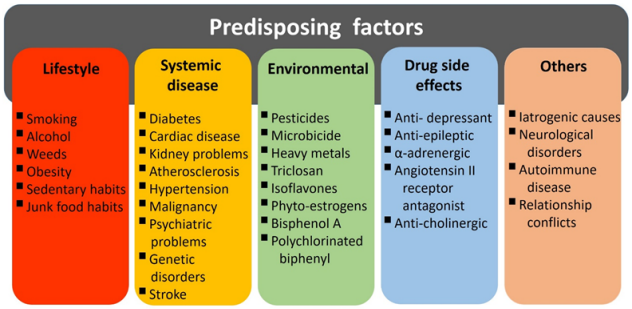
In this review, we tried to elaborately discuss various aspects of sexual dysfunction on both the sexes, epidemiology, risk factors, etiology, pathophysiology, s exual response cycle and associated dysfunctions, treatment modalities, alternative medicines and disease management with herbal supplements and nutraceuticals, their modes of action etc. This review throws special light on erectile dysfunction owing to its high prevalence around the world.

Epidemiology

Ample data from survey on prevalence of sexual dysfunctions are available, but with a lot of heterogeneity among the studies in all aspects like study design, selection criteria, inclusion and exclusion criteria, definition of SD, population age groups and socio economic status and so on. A comprehensive analysis of literature review done by Fourth International Consultation on Sexual Medicine (2015) reported that Hypoactive sexual desire was the most prevalent SD among women and ED among men[22]. There are so many factors that determine the vulnerability of an individual or a population to sexual problems. An old survey conducted in the US found a correlation of SD with race and ethnicity of the population. It was generally observed that on both the sexes, SD is more prevalent in blacks than in whites and Hispanic subjects [23]. Another population based cohort study in Brazil also showed the same observation for ED i.e., 89 incidence per 1000 person-years in black compared to white (61.7) and mixed (60.7) population. For ED, the same study estimated the crude incidence of 65.6 cases per 1000 person-years, also with higher correlation to age, lower education and chronic diseases [23]. Although it is a well-established fact that age and chronic health conditions are general risk factors for ED, little is known about the incidence and exact mechanisms of how they correlate with each other. Surveys conducted 2 decades ago have found a clear correlation between erectile dysfunction and factors like educational and socioeconomic status too [24]. Study conducted by National Health and Nutrition Examination Survey (NHANES) on 2126 adult males of mixed age groups showed that nearly 18.4% of men (i.e., about 18 million men in the US) were affected by ED and the prevalence positively correlated with age. Even 5.1% of young men in age group 20-39 suffered from ED [3].

The largest study done in the US till date (survey done in 31,581 female respondents aged 18 years and above) showed the prevalence of any sexual problem (desire, arousal or orgasm) was 43.1%; with desire problems with maximum prevalence of 37.7%. These results correlated well with age of the subjects [25]. Recent survey done in 400 randomly chosen women from age 18-50 years from western Iran reported that 46.2% of them reported FSD with 45.3% with desire problem, 37.5% with arousal problem, 41.2% with lubrication problem, 42.0% with an orgasm problem, 44.5% with a satisfaction problem and 42.5% with coital pain. Interestingly this survey revealed that the prevalence was inversely proportional to the educational status of the subjects and directly correlated with age [26]. Systematic review of the literature from 2000 to 2014 and meta-analysis of 95 international studies showed that 41% of premenopausal women report FSD [27]. Another study conducted in 586 Chinese women (age range of 22–60 years) estimated that 37.6% women reported FSD, most prevalent of which was orgasmic problems in 36.8% subjects [28]. Although there are so many surveys done on mixed, random and infertile females, a very few them focused on looking at FSD prevalence in fertile female subjects. One such study conducted in India brought out a surprising and alarming fact that nearly half of the fertile women reported FSD [29].

Figure 1: Risk factors that predispose to sexual dysfunction.



Predisposing factors

Lifestyle associated factors

Positive impact of food rich in protein, low calorie-high protein, Mediterranean, fibre containing vegetables on endothelial, sexual function and ED have been documented. Obesity and poor physical activity has a well-known link with sexual performance. Very recently, NIH based lifestyle intervention for a period of 6 months by 5–10% reduction in weight or a reduction in body mass index (BMI) below 29 kg/m2 has shown an improvement in the total McCoy Female Sexuality Questionnaire (MFSQ) of women reporting intercourse [30]. A 2 year-long study conducted in Italian men who have ED or with increasing risk of developing ED clearly showed a strong restoration of erectile function. The erectile function score (International Index of Erectile Function-5 [IIEF-5] drastically improved in men with 2 year-long lifestyle intervention [31]. Chronic and persistent alcohol consumption, smoking (both

active and passive), weeds like cannabis etc., have been well documented to have a pronounced negative impact on sexual health irrespective of all the other predisposing factors.

Systemic disease

Diabetes mellitus

WHO report states that the number of people with diabetes has shot up steeply from 108 million (1980) to 422 million (2014) in the last 3 decades [32]. This also implies that diabetes associated ED is also proportionally increasing every year. The estimates of prevalence of ED in diabetic men is a broad figure ranging from 20% to 85% and not an absolute one owing to the differences in study designs, inclusion/exclusion criteria, demographic variations, assorted methods of result analysis etc. [33]. The pathophysiology of how diabetes promote sexual dysfunction is not well understood but for some studies that show that diabetes impairs endothelium dependant relaxation of penile smooth muscles. Advanced glycation end-products (AGEs) are higher in diabetes patients and are found to have a negative role in endothelial NO mediated smooth muscle relaxation and this could be one of the major reasons for high prevalence of ED in diabetic patients [34].

A study done in limited European women subjects with type I diabetes clearly showed their predisposition to sexual problems majorly in the arousal phase like decreased desire and dyspareunia. This correlation was also found to be dependent on psychological factors in these diabetic women. 27% of diabetic women and only 15 % of non-diabetic control women reported sexual dysfunction establishing a clear and strong correlation to type I diabetes and female sexual problems [35]. Another survey done in Iranian women with type II diabetes showed that 78.7% of them reported problems in multiple aspects of sexual response cycle [36].

Cardiovascular disease (CVD)

The association of heart disease and sexual dysfunction, especially ED is well established from the reports obtained from CVD patients. Prevalence of ED in coronary artery disease patients (CAD) was found to be 76% in a study conducted in India on nearly 180 CAD patients with increase in risk with increasing number of problematic vessels [37]. Another study showed a figure of 47% for overall ED prevalence among CAD patients compared to 24% in controls [38]. Although the pathophysiology of the condition is multifactorial, they share some common routes. For example, both arise from blood flow restriction in endothelium [39]. The association might stem from one or more of the following reasons: (a) Decreased blood flow to corpus cavernosum muscle due to arterial insufficiency (b) Reduced availability of endothelium derived NO causing reduced vasodilatory response in penile vessels (c) Imbalance between vasodilatory and vasoconstriction agents like prostacyclin, endothelin etc.[40]. Apart from the direct effect of CVD, there are problems that arise as side effects caused by drugs used by CVD patients. On the other hand, the studies done to understand the correlation between CVD and female sexual dysfunction is very scarce except for a few that report nearly 43.1% prevalence [41].

Chronic kidney disease (CKD)

The major problems in women with CKD is hormonal imbalance, menstrual irregularities, amenorrhea, lack of vaginal lubrication etc. The mostly accepted and well explored pathophysiology is through prolactin levels in CKD patients. As a consequence of increased production, decreased clearance and CKD mediated dopaminergic inhibition, the levels of prolactin remains elevated in people with renal failure [42]. Higher prolactin levels results in decreased secretion of gonadotropin releasing hormone (GnRH), resulting in reduced leutinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol release, eventually culminating in impaired ovulation and also sexual dysfunction [43]. Hyperprolactinemia is also considered a major causative condition resulting in ED owing to its direct impact on the levels of serum testosterone [44]. A massive cross-sectional study conducted by Harvard school of public health conducted on more than 30,000 men determines the prevalence of ED among CKD patients to be 33% [45]. Another study done in Turkish men estimates the overall prevalence to be 69.2% [46]. A meta- analysis that reviewed 50 independent unrelated studies calculates the average prevalence to be 70% [47].

Atherosclerosis

Animal experiments in female rabbit have clearly demonstrated that atherosclerosis in hypogastric-vaginal/clitoral arterial bed leads to diminished clitoral erection and also negatively impact vaginal engorgement [48]. In contrast to very scarce knowledge and data for female sexual dysfunction, impact of atherosclerosis in male sexual function, especially ED is quite well studied. Most men with ED have risk factors for atherosclerosis like high **cholesterol** levels, smoking, high blood pressure, diabetes, obesity etc. Any form of atherosclerosis in penile arteries will eventually narrow the arterial wall, which in turn reduce the blood flow into the cavernous area hampering penile erection. Sodium fluoride based uptake method to detect the lipid plaques in artherosclerotic lesions along the arterial walls has effectively established the risk of artherosclerotic patients to vascular ED [49].

Hypertension

Data from 2015 states those 1 in 4 men and 1 in 5 women had hypertension according to the WHO estimate [50]. This figure is quite alarming mainly due to the fact that hypertension is one of major risk factors of other morbid systemic diseases like CVD, CKD, stroke, DM, dementia etc. In a mass survey conducted in more than 7689 patients, 3906 had hypertension alone without any other systemic disease and in this group, ED was found to be prevalent in 67% using Sexual Health Inventory in Men (SHIM) questionnaire [51]. Jensen et al. observed that among the hypertensive patients who reported ED, 89% was due to penile circulation disability [52]. It is hence a very obvious link between blood flow and penile erection given the inevitable fact that erection is dependent on smooth blood flow in the penile arteries with right amount of pressure.

Psychiatric conditions

Depression has a negative impact on sexual function according to a Britain based survey [53]. There is an alarming prevalence (60-80%) of sexual dysfunction in women with schizophrenia [54]. 80.6% in a Chinese study [54]; 74% of men and 82% of women suffering from schizophrenia report some form of sexual dysfunction [55]; 45.3% of the schizophrenic men report sexual dysfunction in a US based study [56]. The major problems with psychiatric patients is their regular intake of anti-depressants and anti-psychotics that severely impact sexual functions. Reports from meta-analysis found that nearly 80% of patients under anti-depressant treatment reported sexual dysfunction; men with higher rates of desire and orgasmic dysfunction than women and women with higher arousal dysfunction than men [57]. Drugs like serotonin reuptake inhibitors and anti-dopaminergic drugs, serotonin norepinephrine reuptake inhibitors, Monoamine oxidase inhibitors have wellknown negative impacts on sexual functions at different levels majorly affecting the sex hormones.

Malignancy

There are four major factors that make the cancer patients susceptible to sexual dysfunction. (i) Cumulative effect of anaemia, anorexia, change in metabolic activity, homeostasis etc. (ii) Psychological problems associated with cancer such as anxiety, depression etc. [58] (iii) Side effects caused by cancer therapies like chemo, radio, surgery etc. [59] (iv) anatomical problem caused at the cancer site i.e., if the cancer originates in one of the reproductive/sex organs and tissues like cervical, testicular, ovary, prostate, vaginal etc. In any of the above cases, irrespective of genders, the normal sexual functioning of the individual is compromised.

Genetic risk factors

Sickle cell anaemia: Serum testosterone levels in Sickle cell di sease (SCD) patients is markedly reduced compared to healthy people [60]. Hypogonadism is observed as a very common trait in SCD patients [61]. Hypogonadism arises due to low levels of serum FSH and LH, indicating that testicular dysfunction is the central etiology of the correlation [62].

Thalassemia: A study done in 168 thalassemia patients showed that the prevalence of hypogonadotropic hypogonadism was 76.2% with poor semen quality with drastic decrease in sperm count and percentage motility [63]. For females, the major aspect affected in thalassemic women is the imbalance between generations and scavenging of reactive oxygen species (ROS) resulting in oxidative stress apart from hypogonadism [64]. This manifests in several aspects of fertility and reproduction.

SNPs: Recently a single locus in chromosome 6 called SIM1 has been implicated directly in ED in a huge genome wide survey on 222,358 men [65]. SIM1 is a transcription factor belonging to the family of leptin–melanocortin system that is known to take part in sexual functions.

Environmental factors

Impotency was reported in four out of five farmers who extensively used pesticides and herbicides in agriculture already five decades ago[66]. The negative impact of chemicals used for agriculture on sexual health was known from centuries. Organophosphorus insecticides like parathion, malathion, phosalone, chlorpyrifos, reversible inhibitors of Acetylcholinesterase (AChE) have been shown to induce the production of ROS and hence cause reproductive tissue damage [67]. A broad range of pesticides like herbicides, fungicides, insecticides, termiticides etc. have been identified as potential endocrine disruptors. Cadmium is a common toxic metal commonly present in industrial workplaces and is also a well-known endocrine disruptor. Cadmium on short exposure was found to impair leydig cell regeneration and also reduced hormones like FSH, LH and testosterone [68]. Studies done in fruit flies have shown that methylmercury, another hazardous metal induced oxidative stress and also brought down the triglyceride levels [69]. Triclosan, a very commonly used anti-microbial agent present in toothpaste, soaps, detergents etc. was shown to repress testicular steroidogenesis [70]. Soy derived isoflavones like diadzin and genistin are abundant in soy and identified as well-known phytoestrogens that have endocrine altering properties [71].

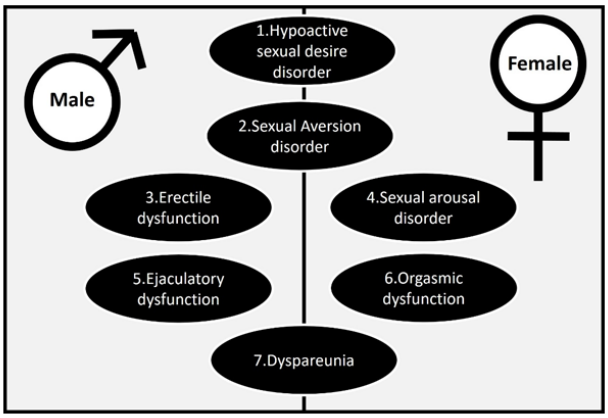
Side effects caused by drugs

Drugs that are used for management of hypertension (Alpha adrenergic drugs such as clonidine and prazosin[72,73], angiotensin II receptor antagonist like valsartan[74], aldosterone receptor blocker spironolactone [75] have established mechanisms of hampering sexual response cycle at different levels. Anti-depressant drugs like paroxetine- serotonin re-uptake inhibitor [76], moclobemide- monoamine oxidase inhibitor [77] etc. and anti-epileptic drugs like gabapentin [78] have been implicated in severe sexual dysfunction and impotence.

Other risk factors

Erectile dysfunction involves the active participation of several autonomic and somatic nerves and hence both the genetic (myotonic dystrophy, spina bifida, kennedy disease, parkinson's disease etc.) and acquired neurological disorders (Head and spinal cord injuries, epilepsy, multiple sclerosis etc.) predisposes an individual to sexual problems [79]. A recent study done in Italy on 326 neurological patients, 38.6% reported ED [80]. High prevalence of sexual problems are observed in other conditions like rheumatic disease [81], gastrointestinal disease [82], psoriasis [83], chronic liver disease etc. [84]. Pelvic surgery, radiotherapy, psychotropic drugs, retroperitoneal lymph node dissection are some of the iatrogenic causes that predispose an individual to various forms of sexual disorders like ED and ejaculation related problems [79]. Although it is a cliché term, sexual problems that stem from relationship related issues is very common and can be addressed with couple counselling and psychotherapy. Relationship conflicts are also known to negatively impact the therapeutic outcome of sexual problems.

Figure 2: Various forms of sexual dysfunctions.



Sexual dysfunction in every stage of sexual response cycle namely: Desire (1, 2 are common to both genders), Arousal (3, 4 are specific to genders), Orgasm (5, 6 are specific to genders) and Pain (7 is common to both genders).

Types of sexual dysfunction

People of all ages suffer from some form of sexual dysfunction; but is more pronounced in older men and women. Unlike other diseases that grab our immediate attention, sexual problems are considered a stigma and are often unnoticed, unreported or untreated. 'Sexual dysfunction' is a very broad umbrella term that refers to one or more than one problem faced either in sex life or fertility. Some are common to genders and some are gender-specific as depicted in the Fig 2. Starting from libido, the term covers a vast subset of problems encountered during, orgasm, coitus, ejaculation, fertilization etc. Within sexual response cycle, the problem can be associated with desire, arousal, orgasm and pain.

Hypoactive sexual desire disorder (HSDD)

In 2013, Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) defined HSDD in men by two criteria: A—"persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" and B—"marked distress or interpersonal difficulty" [85]. In women, HSDD is defined by monosymptomatic criteria that merge the aforementioned 2 separate criteria [86].

The *International Classification of Disease* (ICD-11) includes a diagnostic code for HSDD as an "absence or marked reduction in desire or motivation to engage in sexual activity as manifested by any of the following:

- reduced or absent spontaneous desire (sexual thoughts or fantasies);
- reduced or absent responsive desire to erotic cues and stimulation
- inability to sustain desire or interest during sexual activity" [87].

Although genetic, social and psychological factors impact the desire to engage in sexual activity, the key players in the process are neurotransmitters and hormones. Two pathways that operate and control sexual desire are 'excitatory' and 'inhibitory'. External (audio-visual, images, odors like pheromonal etc.) or localized cues (in external genitalia) trigger arousal through the integrity and right balance between excitatory and inhibitory factors. Excitatory neurotransmitters include dopamine, melanocortin, noradrenaline and oxytocin and inhibitory neurotransmitters include serotonin, opioids and endocannabinoids. Particularly levels of neurotransmitters like endocannabinoids that mediate sedation and serotonin that mediate sexual satiety are kept under check. The activation of excitatory neurotransmitters in hypothalamus and limbic region subsequently reduces the inhibitory neurotransmitters in hypothalamus, limbic region, cortex and mid-brain. Hormones like testosterone, estradiol and progesterone enhance sexual function and cortisol has the opposite effect.

In women, the sexual desire and arousal are heavily influenced by the phase of menstrual cycle. Generally it is considered to increase steeply a week before ovulation and shoots up during ovulation [88].

Ejaculatory disorders (EjD)

The physiology of ejaculation is intensely complex and involve an orchestrated and well-co-ordinated action of neurotransmitters, hormones and several neural circuits. It starts in the sympathetic nerves through alpha-adrenergic receptors leading to contraction in seminal vesicles and prostate followed by semen emission into the posterior urethra, while the bladder neck remains closed to prevent the retrograde semen flow into the bladder.

EjD occurs due to problems in one or more stages of ejaculation namely semen emission followed by semen expulsion culminating in pleasant sensation (orgasm) in the brain centre. The latest revised version of International Classification of Diseases (ICD-11) in 2018, categorized EjD into 5 types namely: (i) Male early ejaculation (ii) Male delayed ejaculation (iii) Retrograde ejaculation (iv) Other specified ejaculatory dysfunctions (v) Unspecified ejaculatory dysfunctions [89]. However in broader sense, EjD can be classified as (a) Premature (early) (b) Delayed (late) (c) Retrograde (d) Anejaculation. Anxiety and other psychological factors might cause premature ejaculation, which is very common among all the ejaculatory disorders. The semen is ejected very quickly after vaginal penetration leaving no time for orgasm. Local anaesthetics like Lidocaine and Prilocaine are used to manage the condition by reducing sensitivity in penis. Behavioural therapy is also a choice of treatment for early ejaculation problems [90]. Delayed ejaculation is a condition where the semen expulsion takes a very long time since the time of stimulation leading to frustration for the partners. It arises from several factors like drug and alcohol abuse, diuretics, depression etc. and is primarily dealt by psychotherapy and counselling. Retrograde ejaculation is characterized by the expulsion of part or whole of semen into bladder and is diagnosed by the presence of semen in urine. This condition is majorly not treated unless it culminates in infertility, where semen is retrieved and used for in vitro fertilization (IVF) t

echniques. Anejaculation, the absence of ejaculation can either be total(completely absent) or 'situational' (at certain times) and is normally treated with psychotherapy.

Erectile dysfunction (ED)

Erection is an active and complex neuro-hemodynamic process and is categorized into one of the three types based on the stimuli involved namely, nocturnal, reflexogenic and psychogenic. The sequence of nerve stimulation precisely the afferent and efferent pathways depends on the aforementioned type of erection. In any case, the interplay between central and peripheral neural circuits control the sexual activity in men and women, although central mechanisms are less well explored compared to peripheral. The medial preoptic area (MPOA) in hypothalamus is the epicentre of sexual response. The electrical stimulation studies have proved that MPOA and paraventricular nucleus (PVN) are 2 inevitable regions that elicit a sexual response. In psychogenic erection, the excitation of specific areas in hypothalamus descends to parasympathetic neurons in sacral spinal cord (S2-S4), from where the somatic nerves exit the central nervous system and reach the penis through pudendal nerves. On the contrary, in reflexogenic erection, the sensory stimulations from the genitalia (perianal, scrotal, perineal, penile etc.) travel to the sacral centre of spinal cord via pudendal nerves. From the sacral centre itself, the motor pathways reached the penis via pelvic and cavernous nerves etc. [91]. The vipergenic pathway and nitrergenic pathways in specific neurons release acetylcholine (Ach) and Nitric oxide (NO) respectively that enable the smooth muscles in corpus cavernosum to relax and attain erection. The non-adrenergic non-cholinergic (NANC) fibres secrete NO and long cholinergic fibres secrete acetylcholine. Ach is found to have a modulatory role that enables the NANC fibres to secrete NO from L-Arginine and it also inhibits the noradrenaline release from the sympathetic fibres until the erection is achieved.

Neurotransmitters in erection

Dopamine

Dopamine, a simple catecholamine is well-known as a neurotransmitter and sex hormone, which exerts its activity either excitatory or inhibitory, depending on the type of receptor and the ion channels opened subsequently. In central nervous system, it is mostly confined to MPOA and PVN of hypothalamus. Intravenous injection of apomorphine, a dopaminergic agonist in rats demonstrated that dopamine, at various levels controlled the erectile response both at supraspinal and spinal sites [92]. Dopamine receptors are broadly classified into 2 subclasses D1 and D2 with a few other subtypes belonging to the seven-pass transmembrane G-protein coupled receptor superfamily. The dopamine mediated response is primarily decided by the receptor subtype it is bound to. In the PVN, dopamine activates the oxytocinergeic neurons probably by Ca2+ influx into cell bodies and subsequent NOS activation that release NO. NO, another neurotransmitter helps in activating the oxytocinergic neurons in the extra hypothalamic sites like spinal cord, independent of guanylate cyclase activation [93].

Oxytocin

Oxytocin, the neuropeptide hormone has autocrine and paracrine effects in various reproduction processes in both male and female. In the context of penile erection, it is a well-established inducer. Apomorphine (dopamine agonist) also activates oxytocinergic neurons in the PVN i.e., Apomorphine induced penile erection is mediated by oxytocin [94]. Induction of penile erection by injection of oxytocin in the ventral tegmental area (VTA) of male rats was subsequently abolished by co-injections with either of oxytocin antagonist (vasotocin) or a neuronal NO synthase inhibitor or a N-type Ca2+ channel blocker. This clearly demonstrated that oxytocin worked in combination with NO mediated pathways in the dopaminergic neuron in penile erection [95].

Serotonin

Serotonin (5-hydroxy tryptamine), a monoamine neurotransmitter exerts facilitatory or inhibitory roles in penile erection depending on the receptor type involved. The pharmacological action of serotonin is at both supraspinal and spinal sites participating in both sympathetic and parasympathetic pathways. Treatment of rats with 5 HT2c recept or agonist m chlorophenylpiperazine induced penile erection showing higher concentration of prolactin and corticosterone in plasma [96]. Treatment with selective serotonin re-uptake inhibitors (SSRIs), like paroxetine led to increase in the amounts of serotonin at the synapse causing erectile dysfunction probably via the neuronal NOS (nNOS) production [97].

Nitric oxide (NO)

Unlike other neurotransmitters, NO is in gaseous form and is neither stored in vesicles nor released by exocytosis, but merely diffuses from the synapse on demand. Also unlike others, it is not a stringent neurotransmitter rather has a neuromodulatory action. NO synthesized by either of the three isoforms of NOS (endothelial- eNOS, neuronal- nNOS, inducible- iNOS) have completely different roles depending on the origin and target cell type. One is its well-explored participation in NO-cGMP signalling in the smooth muscles, where it binds to its target gyanylate cyclase generating cGMP. Penile erection is achieved via cGMP mediated phosphorylation of various kinases and ion channels that results in myosin light chain (MLC) dephosphorylation [98]. Another less-dissected role of NO is its neuro-modulatory roles in discrete locations like MPOA and PVN. Centrally released NO is associated with the release of other neurotransmitters; however the molecular mechanism behind this is not fully understood [99]. It is probably due to the S-nitrosylation of the receptors of neurotransmitters [100], or by regulating the efficiency of transport proteins in synaptic cleft by its mere presence [101] or by cGMP mediated protein phosphorylation.

Acetyl choline (Ach)

Although there are no convincing data on the role of Ach in CNS, its direct positive role on penile erection is very convincing from the results obtained from intracavernous injections in monkeys [102]. Two possible mechanisms by which it impacts penile erection could be (i) It enables the release of NO in

endothelium [103] (ii) supresses the release of norepinephrine from adrenergic nerve terminals [104].

Glutamate

Glutamate, the excitatory neurotransmitter binds to N-methyl-D-aspartate (NMDA), which is an ion channel receptor that gets activated on glutamate binding. Microinjection of NMDA antagonist MK-801 into the MPOA site impaired copulatory behaviour in male rats [105]. Glutamate is released into the MPOA during coitus, especially during ejaculation. Microinjection of L-Glutamate in MPOA increased the intracavernous pressure (ICP) comparable to the electrical stimulation of MPOA indicative of penile erection [106].

GABA

Apomorphine (dopamine agonist) mediated dose dependent penile erection in rats was compensated by pretreatment of animals with GABA-A agonist muscimol or the GABA-B agonist baclofen or both [107]. Another experiment showed that the muscimol effect is abolished by bicuculline, a GABA-A receptor antagonist [108]. These animal studies together imply the inhibitory role of increased GABAergic activity in PVN on penile erection.

Androgen

Role of androgens in sexual desire and erection is a highly controversial and heavily debated topic with a number of contrasting findings from several researchers. Our literature review strongly supports the role of testosterone in various aspects of sexual response cycle especially in penile erection. In a cohort of more than 400 older men (58 years mean age), topical testosterone gel administration resulted in improvement of desire, nocturnal erections and efficiency of coitus [109]. In patients with organic ED, a positive correlation was observed between free testosterone levels and in the trabecular smooth muscles in corpus cavernosum irrespective of age of the patients, establishing a clinical significance to the amounts of testosterone [110]. Results obtained from the same research group showed that transdermally applied testosterone improved penile erection in men with arteriogenic ED, who responded poorly to sildenafil treatment [111]. Studies showed that testosterone stimulated the pharmacological response to sildenafil alone [112] or sildenafil and apomorphine in severely hypogonadal men [113]. However it is noteworthy that testosterone is a temporary saviour for ED on sildenafil-non responders but may not help in completely or permanently curing ED. This was evident from the study done on testosterone deficient men, whose erectile function improved during the first month of testosterone therapy and declined subsequently [114].

There are a handful of human and animal experiments that explored the role of androgens in maintaining anatomical structures that help and promote penile erection. Androgen deprivation in rats led to apoptosis of corpus cavernosum and replacement of apoptotic cells by irregular collagen fibers [115]. Similarly, androgen deprivation in rabbits significantly reduced intracavernosal pressure and trabecular smooth muscle content and the effect was reversed and restored with androgen supplementation [116]. Studies carried out in rabbit model and mouse pluripotent stem cells have demonstrated that testosterone is important in proliferation of stromal progenitor cells into myogenic lineage rather than adipocyte lineage probably via an androgen receptor mediated pathway [117].

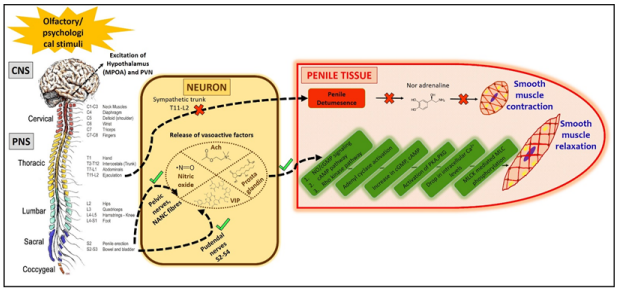
Female sexual arousal disorder

DSM-IV-TR diagnostic criteria for Female Sexual Arousal Disorder (FSAD) is "Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity an adequate lubrication-swelling response to sexual excitement" [118]. Apart from the primary psychological factors, this condition might stem from one of the many factors like less or no vaginal lubrication or reduced clitoral and/or labial sensation or reduced smooth muscle relaxation in vagina or reduced engorgement of clitoris and labium etc. Prior trauma, injury, surgery, medication etc. are common etiologies [119].

Pain disorder

Painful intercourse or dyspareunia is common for both the genders. Dyspareunia in women might be caused by lack of lubrication, infections, injury, inflammation, parturition and sometimes congenital. The pudendal nerve is located in such an anatomical position in pelvis that it is easily prone to damage during surgeries and other injuries. Pudendal nerve accounts for most of the pelvic pain and has to be examined first for diagnosis. Decrease in circulating estradiol concentration in aged women is a major cause of vaginal dryness causing dyspareunia [120]. In men, etiology and risk factors include injury, chronic use of psychotic drugs, infection, psychogenic and other iatrogenic causes. Scar tissue formed post injury or infection in male sex ducts and glands is a common cause of pain during ejaculation, as is the case with Peyronie's disease [121].

Figure 3: Molecular pathways behind smooth muscle relaxation.



The psychogenic erection begins with sensory and psychological cues at the CNS in the MPOA and PVN and descends through the peripheral nervous system along the spinal cord to the parasympathetic neurons in sacral spinal cord (S2-S4). Stress induced stimulation of sympathetic nerve (hypogastric nerve from T11-L2)) leads to penile detumescence. Ach modulates the release of NO from NANC fibres and prevents the release of noradrenaline from sympathetic nerves until erection is achieved. The pudendal nerves exit the spinal cord at S2-S4 and the reflex stimulation travels to penis via pelvic and cavernous nerves etc. Various vasoactive agents like Ach, NO, VIP, Prostaglandin etc. are secreted by both neuronal and

endothelial tissues and upregulate the NO/cGMP pathways and cAMP pathways in the penile microenvironment. Adenyl cyclase get activated and there is an intracellular accumulation of cAMP and cGMP, which in turn results in the activation of various proteins like kinases and ion channels that decrease the intracellular Ca2+ levels aiding in Myosin light chain phosphorylation culminating in penile smooth muscle relaxation and erection. Abbreviations: CNS- Central Nervous System, PNS- Peripheral Nervous System, MPOA- Medial Pre Optic Area, PVN- Para Ventricular Nucleus, NANC- Non-adrenergic non-cholinergic, Ach- Acetyl Choline, VIP- Vasactive Intestinal Peptide, NO- Nitric oxide, cAMP- Cyclic Adenosine Monophosphate, cGMP- Cyclic Guanosine Monophosphate, PKA- Protein kinase A, PKG- Protein kinase G, MLCK- Myosin Light Chain Kinase, MLC- Myosin Light chain.

Molecular pathways behind Smooth muscle relaxation

What are smooth muscles and how do they differ from other muscles of the body? Smooth muscles are derived from the mesoderm and neural crest cells and are non-striated unlike cardiac and skeletal muscles and are involuntary in action i.e. its contraction is not in response to conscious effort, rather due to reflex effect as a response to various autocrine/paracrine hormones, neurotransmitters and vasodilators, chemical agents etc. Multiple layers of smooth muscles line the inner layer of organs like stomach, intestine, vascular walls, heart, kidney, bladder, eye, reproductive structures like vagina, penis etc. most of where they perform most inevitable 'housekeeping' activities. Smooth muscle cytoplasm is rich in actin and myosin cytoskeleton helping it to contract and relax [122].

NO-cGMP signaling (Nitrergic pathway)

Nitric oxide (NO) released from nonadrenergic-noncholinergic cavernous nerve terminals in the genital vascular system is produced by nitric oxide synthase (nNOS)[123]. The released nitric oxide diffuses into the smooth muscle membrane and binds to the heme moiety of soluble guanylate cyclase (sGC) and activates sGC which generates second messenger cGMP from GMP. The intracellular cGMP directly binds and activates serine/threonine protein kinase like protein kinase G (PKG), which in turn phosphorylates several membrane bound ion channels, proteins that can reduce the intracellular Ca2+ levels. With the drop in intracellular Ca2+ levels, free Ca2+ is no more available to bind to Calmodulin leading to corpus cavernosum and spongiosum muscle relaxation. On the contrary, when the intracellular free Ca2+ is abundant, the Ca-calmodulin complex activates myosin light chain kinase (MLCK), which can in turn phosphorylate myosin light chain in presence of ATP. This phosphorylation leads to cross-bridges between myosin and actin cytoskeleton leading to smooth muscle contraction [122].

RhoA/Rho Kinase pathway

Extensive research on erectile physiology has identified that at normal times, penile muscles are maintained anatomically constricted with the help of RhoA/Rho Kinase pathway. Active RhoA/Rho Kinase pathway ensures to keep the muscle tone contracted by keeping the Myosin Light Chain Phosphotase in its inactive form i.e. phosphorylated MLC (MLC-P). During sexual phase, the NO/cGMP signaling is triggered and it suppresses the RhoA/Rho Kinase pathway through cyclic GMP-dependent protein kinase (PKG) to enable the relaxation of smooth muscles [124].

cAMP pathway (Vipergic pathway)

cAMP pathway is another cyclic nucleotide dependant signalling pathway that operates in parallel to the NO/cGMP signalling in keeping the muscle tone relaxed. Eicosanoids like prostaglandins and vasoactive intestinal peptides (VIP) bind to their receptors called GPCRs, and activate adenyl cyclase (AC) accumulating intracellular cAMP. Intracellular levels of cAMP are decided by balance between adenyl cyclase (AC) and phosphodiesterase (PDE) enzymes. Protein kinase A (PKA) is the best studied target of cAMP and is known to bind to several cellular targets like PDE, myosin light chain kinase, PKG etc. and phosphorylate them. cAMP is known to crosstalk with NO/cGMP signalling through direct activation of PKG [125].

Management of sexual dysfunction

Treatment strategy totally depends on what kind of sexual disorder is being diagnosed and during treatment; the physician should take into account so many factors including age, genetic background, duration and severity of problem, presence of systemic disease and malignancy etc. The problem with treating sexual dysfunctions is, it is often interlinked with so many other systemic diseases and hence due to this high prevalence of comorbidity, the treatment regimen be made keeping the medical records of the patient in consideration.

Pharmacotherapy

PDE5 inhibitors are the most popular first-line class of drugs given for erectile dysfunction and male impotence. Sildenafil (Viagra), originally developed for treating hypertension, was serendipitously identified to induce penile erection during clinical trials. Since the discovery of sildenafil in 1998, several other sister drugs like vardenafil (**Levitra**, 2003), **tadalafil** (**Cialis**, 2003) and **avanafil** (Stendra, 2012) have developed. These PDE5 inhibitors have structural similarity to cGMP; hence bind to PDE5 enzyme and inhibit cGMP hydrolysis, thus amplifying the magnitude of NO-cGMP signalling, paving way to a prolonged erection. Although these drugs are proven effective, they are generally associated with mild to adverse side effects like nausea, hypertension etc. Hence for suitable cases, PDE5 inhibitors are combined with nitroglycerin or alpha-adrenergic blockers to reduce blood pressure [126]. Vision [127] and hearing loss [128] have also been reported as adverse effects of PDE5 inhibitors. After PDE5 inhibitors, the next promising target looks like melanocortin receptor. Melanocortin receptor has recently emerged as the top priority target for pharma companies majorly owing to the recent discovery of close association between SIM1 locus and ED [65]. Alprostadil (synthetic prostaglandin E1) available as intraurethral injection

and cream acts through production of more cAMP in smooth muscle [129]. Other targets under research and clinical trials for penile erection include Rho kinase inhibitor (like Y-27632), dopamine agonist like (like ABT-724), soluble guanylate cyclase activators (like BAY 60-4552) etc.

Catecholamines like epinephrine (adrenaline) and norepinephrine (noradrenaline) bind to a class of GPCR family of transmembrane proteins, activation of which leads to smooth muscle contraction through increase in intracellular Ca2+ level. Modulation of this pathway by using adrenergic receptor antagonists like phentolamine have been constantly tried by several researchers both for female and male sexual dysfunction, however none yet approved for this purpose by FDA.

For hypoactive sexual desire disorder (HSDD), Flibanserin (Addyi) was the first ever drug approved for HSDD in 2015. It is a serotonin receptor agonist and antagonist and is claimed to act through serotonin receptors, lowering its levels and subsequently increase dopaminergic neurons [130] still remains debated for its efficacy and side effects [131]. In June, 2019, the U.S. FDA approved Vyleesi (bremelanotide) to treat hypoactive sexual desire disorder (HSDD) in premenopausal women. Vyleesi activates melanocortin receptors, but the mechanism by which it improves sexual desire and related distress is unknown. Anti-depressants like brupropion (wellbutrin), which are serotonin reuptake inhibitor, have been useful in increases sex drive and sexuality in certain women [132].

Ospemifene (Osphena) is an estrogen receptor modulator approved by FDA in 2013 for treating dyspareunia in women patients with vulvovaginal atropy. Its exerts estrogenic effects by decreasing the pH of vagina and reduce vaginal dryness [133]. Vaginal dryness is also modestly treated with topical application of estrogen/estradiol creams (premarin®, estrace®), tablets (vagifem®) and vaginal rings (estring®), however it doesn't help with HSDD. In this context, it is important to mention that there are no FDA approved testosterone drugs for treating HSDD or any form of sexual dysfunction in women and are generally prescribed off-label [134].

Surgical options

Erectile dysfunction is probably the only known sexual dysfunction that might require a surgical approach for treatment depending on the etiology and severity of the condition. Surgical option is sought for ED to either (i) cause erection, (ii) maintain erection or (iii) facilitate erection by increasing blood flow by reconstructing arteries or blocking veins. Semi-rigid malleable rods, inflatable penile prosthesis, penile arterial revascularization, venous infusion of erectogenic agents etc. are some commonly adapted hospital procedures for management and treatment of penile erection [125].

Psycho and physiotherapy

Like for some psychological disorders, cognitive-behavioural therapy (CBT) is the most commonly used management method. Most of the reference for CBT goes to the pioneering research done on sexual therapy by Masters and Johnson [135]. Key aspects of CBT are (i) Education, (ii) sensate focus, (iii) stimulus control, (iv) sexual skills training, and (v) cognitive restructuring [136]. Physiotherapy is another combined treatment methodology used by healthcare professionals for both men and women experiencing pelvic pain during coitus especially women with vaginismus and dyspareunia [137].

Alternative medicine

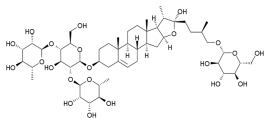
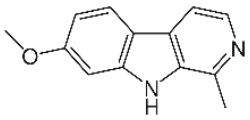
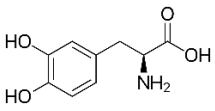
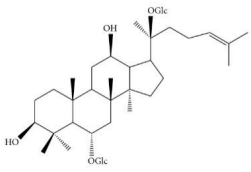
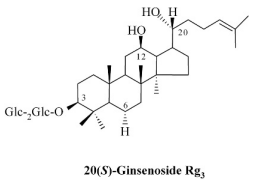
Like any other illness, from centuries human being relied on natural means of curing sexual problems. Ambrien, a triterpene alkaloid isolated from Sperm whale gut have been used by ancient Arabs for various illness including sexual performance, although only a single research group has scientifically evaluated its role as an aphrodisiac [138]. Traditional Chinese medicine used Buff toad skin as an aphrodisiac, the effect probably is accounted to the presence of 5-MeO-DMT (5-methoxyN, N-dimethyltryptamine) and stands invalidated by scientific evidence till date [139]. On the other hand, plant based aphrodisiacs have gained manifold popularity among public and scientific communities compared to animal based ones. Plant phytochemicals due to their structural similarity to so many metabolites, hormones and neurotransmitters have proven effective in libido enhancement and management of sexual dysfunction in both women and men. For instance L-Dopa from Mucuna pruriens, protodioscin of Tribulus terrestris, ginsenosides from Panax ginseng, diosgenin from Trigonella foenum-graecum, eurycomanone from Eurycoma longifolia etc. are few of the plethoras of phytochemicals well-known as aphrodisiacs. (Refer to table 1). Apart from plant and animals sources, mountain exudates like 'Shilajit' well-known aphrodisiac in Indian traditional medicines like Ayurveda, Unani and Siddha etc. have also gained popularity as Nutraceuticals [140].

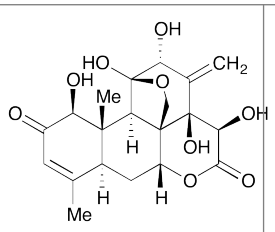
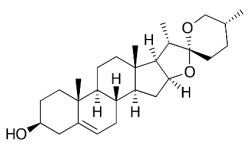
Upcoming surge of Nutraceuticals

Natural home remedies were used from centuries by nearly all the ancient civilizations to cure, mitigate and manage health problems. Owing to their familiarity through generations, lesser side effects, ease of availability and general inclination of the modern man towards organic and natural way of life, Natural medicine has gained more popularity in today's world. In the context of sexual dysfunction, given its stigmatized perception, people resort to Natural and herbal Nutraceuticals. Given the endless array of Nutraceuticals in the online markets, there is a logarithmic increase of their demand with time. Nomenclature and regulatory framework for Nutraceuticals are dealt by countries differently. According to the Dietary Supplement, Health and Education Act (DSHEA) of 1994, Nutraceuticals do not fall under the remit of FDA and are monitored as "dietary supplements". Nutraceuticals are referred as "Natural Health Products" in Canada and are governed by Food and Drugs Authority of Canada. Both functional foods and dietary supplements are referred as "Foods for Special Health Use (FOSHU)" in Japan. The safety and efficacy of functional foods that apply for approval to FOSHU will be evaluated by the Council of Pharmaceutical Affairs and Food Hygiene. Irrespective of the country or region, Nutraceuticals still do not face strict screening and evaluation protocols like drugs, majorly owing to

the fact that they are of natural origin and their labels do not carry exclusive claims to completely cure an ailment.

Table1: Mode of action of selective phytochemicals.

Plant	Active phytochemical	Outcomes	Mode of action	Reference
 Tribulus terrestris	 Protodioscin	Penile erection through smooth muscle relaxation	Protodioscin rich furostenol glycoside fraction may be converted to androgens like testosterone and DHEA	[141]
	 Harmine	Anti-depressant and libido	Monoamine Oxidase Inhibitor (MAO inhibitor) that increases dopamine levels in CNS	[142]
 Mucuna pruriens	 L-Dopa	Libido and improved semen quality	L-Dopa is decarboxylated to Dopamine in CNS. Dopamine inhibits release of prolactin and promotes GnRH, helping in increasing androgens and spermatogenesis	[143]
 Panax ginseng	 Ginsenoside Rg1	Alleviate sexual dysfunction in menopausal women	Exhibit estrogenic activities; but without direct interaction to estrogen receptor	[144]
	 Ginsenoside Rg3	NO production and vascular relaxation	Induced eNOS phosphorylation via ER-mediated PI3-kinase/Akt pathway	[145]
	Aqueous extract rich in ginsenosides	Improvement in testosterone levels, testicular weight and sperm counts	Upregulation of glial cell derived neurotrophic factor (GDNF) as detected with mRNA levels. GDNF has vital role in spermatogonial stem cell maintenance	[146]

 Eurycoma longifolia	 Eurycomanone	Enhanced testosterone steroidogenesis	1. Inhibitory effect on estrogen receptor 2. Inhibitory effect on aromatase enzyme 2. Probably inhibit PDE5 by direct binding (from molecular docking studies)	[147]
	Eurypeptides	Improved AMS score with increased testosterone	Activates CYP17 enzyme to enhance the metabolism of pregnenolone to DHEA and progesterone to androstenedione and to testosterone	[148]
 Trigonella foenum-graecum	 Diosgenin	Increase in testosterone, DHEA-S levels. Improved sperm counts and morphology	Diosgenin conversion to DHEA	[149]

Mode of action of some natural/herbal aphrodisiacs

Yohimbine

Yohimbine is an indolalkylamine alkaloid, derived from Yohimbe (Pausinystalia yohimbe), native to West Africa. As it is a central α-2 adrenergic receptor antagonist, it inhibits norepinephrine release and exhibits an increased cholinergic and decreased adrenergic activity [150]. Its clinical effects include increased penile inflow, reduced penile outflow and increased corpus cavernosum muscle relaxation. Yohimbe is the first plant- derived drug approved by FDA 3 decades ago. Owing to the fact that it was approved by FDA before DHSEA (1994), it is still under FDA approved prescription drug category to treat impotence, in spite of controversies over its efficacy and toxicity. Double-blind, placebo-controlled clinical trial in patients with psychogenic erectile dysfunction showed an improved overall response compared to placebo in terms of sexual arousal, frequency of sexual contact, penile rigidity etc.[151]. Yohimbine was also proven satisfactory in treating men with orgasmic dysfunction [152]. Yohimbine in combination with NO precursor L-Arginine proved effective than placebo and yohimbine alone controls in improving vaginal pulse amplitude response in women with sexual arousal disorder [153].

Korean ginseng

Ginseng has always had the privilege of being a well-known and well-accepted aphrodisiac around the world and mostly referred in the Chinese tradition. The physiological effects are accounted mainly to the ginsenosides, the glycosylated triterpene saponins that probably activate Nitric oxide synthase (NOS) by an unknown mechanism and increase NO levels in rabbit corpus cavernous muscle in vitro. This NO production was specifically abolished in the presence of NOS inhibitor nitro-L-arginine [154]. Another study done in men with oligoasthenospermia (low and slow sperm motility) showed that ginseng extract increased the spermatozoa counts along with increase in hormones like testosterone, luteinizing hormone (LH), dihydrotestosterone, FSH and LH [155]. Effect of the extract were also assessed in menopausal women and showed an increase in FSFI score specifically for sexual arousal [156]. Apart from studies that support direct activation of NOS enzyme by ginsenosides, there are studies that shows the upregulation of receptors like estrogen receptors (in a tissue specific manner), androgen receptor, glucocorticoid receptor etc. by ginsenosides [157]. Studies have reported estrogenic activity by ginsenosides, rather in a receptor independent manner probably through some other upstream targets other than estrogen itself [158].

Fenugreek

Trigonella foenum-graecum (Fenugreek) is majorly associated with women's health in the context of sexual process and ovulation in Indian traditional medicine (Ayurveda)[159]. Estrogenic activities of fenugreek and its primary component diosgenin were demonstrated both indirectly by mammary

gland development [160] and directly by competitive estrogen binding (HAP assay) assays [161]. Testofen®, a unique formulation of fenugreek seeds manufactured by Gencor Pacific Ltd, showed an overall positive physiological response on male libido in a double-blinded randomized study [162]. Furosap™, another protodioscin enriched proprietary formulation of Chereso, NJ, USA was shown to increase serum testosterone levels and sperm profile and libido in healthy volunteers [149].

Tongkat ali

Eurycoma longifolia, well-known in South East Asia often associated with manliness and male virility is long been used by ethnic groups and indigenous people in traditional medicine. Rats fed with root extracts showed high serum and testicular testosterone, FSH, LH and increased spermatogenesis [163]. In silico molecular docking studies and experimental evidence have clearly demonstrated that 'eurycomanone', the major quassinoid accounted for the physiological effects by inhibiting aromatase and PDE enzyme activities [164]. Studies have also proven and indicated that the smooth muscle relaxation induced by E.longifolia might be partly due to the ROCK II inhibitory activity [165].

Velvet bean

Mucuna pruriens is a legume of family Fabaceae, traditionally used by Ayurveda to treat infertility and neurological disorders like Parkinson's disease [166]. The high L-dopa content in seeds makes it an ideal source for extracting the Dopamine precursor L-Dopa to treat parkinson's patients.

Gokshur

The aphrodisiac properties of Tribulus terrestris is majorly attributed to its steroidal saponin 'protodioscin', which was shown to increase serum testosterone, dihydrotestosterone (DHEA) and hormones like FSH, LH, in animals like rabbit, rat and primates [167,168]. Due to the structural similarity to DHEA and owing to the spike in serum DHEA levels after continuous consumption of seed extracts, it is proposed to be converted to DHEA and exhibit androgenic effects [169]. Similar androgenic effects were observed in female who reported sexual dysfunction especially HSDD along with improvement in FSFI index [170].

Horny goat weed

Herba Epimedii is known in Chinese traditional medicine to treat sexual dysfunction apart from a wide range of health problems. The physiological effects are majorly known to be accounted by the presence of icariin, a flavanol glycoside, which upregulated both nNOS and eNOS and also increased serum testosterone at low concentrations in rats that suffered nerve injury [171]. In vitro assays performed on rat smooth muscle cells have shown promising results on the effective inhibition of PDE5 isoforms by icariin fraction obtaind by ethanolic exract of aerial parts of H.epimedii. The surprising aspect of this study was the icariin induced cGMP levels outnumbered NO donor, SNP (sodium nitroprusside) induced cGMP accumulation [60]. Not much studies have been done on human volunteers, however the results obtained from normal male rats and diabetic rats in improvement of penile erection looks interesting [172].

Ginkgo biloba

Commonly called as 'maiden-hair tree' is long been used in chinese traditional medicine to address health issues particularly related to nerves and memory. In vitro experiments performed on porcine arteries revealed the vascular relaxation capacity of Ginkgo biloba extracts in a dose dependant manner [173], the effect was later found to be attributed to its influence on NO production; specifically to its ability to phosphorylate eNOS at site specific to Akt (Ser 1177)[174]. Some preliminary studies also revealed the neuroprotective role of the extract, mainly attributed to its component 'ginkgolides', a terpene fraction that functions as a possible platelet activating factor (PAF) antagonist[175].

Maca root

Maca root plant (Lepidium meyenii), native of Peru Mountains is historically known in South American traditions as a medicinal plant mostly related to sexual desire and fertility. Although there are no clear scientific evidence on its mode of action, there are several active ingredients that are proposed to play some important roles in enhancing sexual behaviours such as macaridine, macamides, macaene, gluosinolates, maca alkaloid etc.[176]. However it is noteworthy that, the observed effects on sexual desire in the clinical trials done so far had nothing to do with androgen and estrogen levels. It is possible that it operates in a different level along the hypothalamic-pituitary axis and needs further exploration.

Shilajit

Shilajit, popular in Indian traditional medicine (Ayurveda) as 'Maharasa', meaning highest order flavour/essence, is a sticky, dark exudate that oozes out from the Himalayan rocks during warm climates. Traditionally known as an anti-aging and rejuvenating medicine, it is also well-known as an aphrodisiac. The bioactive like fulvic acid, humic acid, oxygenated dibenzo-α-pyrone chromoproteins are proposed to account for its pharmacological effects [177]. Experimental evidences have indicated the Shilajit increased central cholinergic pathways and exhibit parasympathomimetic activity and enhance the muscle relaxation through increased response to Ach, thereby contribute to relaxation of rat corpus cavernosum [178]. 90 day consumption of purified shilajit showed increased sex hormones like testosterone, DHEA in randomised clinical trials on healthy volunteers [179].

Nutraceutical market in management of erectile dysfunction and libido – Growth and risks

Market research done by US based BCC Inc. in 2018 states that the global nutraceutical market might reach $336.1 billion by 2023 from $230.9 billion in 2018 with a CAGR of 7.8%. In US alone, more than 50% of the adults buy and consume dietary supplements (DSs) making a profit of $35 billion to manufacturers. A big chunk of this profit is enjoyed by the manufacturers who address sexual problems and libido enhancement. Very recent market research done by UK based

Technavio posted a CAGR of 9% for sexual enhancement supplements during the forecast period 2019-2023; and the key drivers in this market being erectile dysfunction (ED). Another very interesting market analysis done on Amazon products that address ED came up with the information that among all others, the top 5 products contained one of either ginseng, horny goat weed, L-arginine, and tongkat ali in their ingredients [180].

While the companies are making an exponential profit, on the other side of the story i.e., the consumer end still suffer serious threats owing to the callous attitude of the manufacturers, who adulterate the supplements with pharmaceutical ingredients to make profitable and consistent business. From 2007 to 2016, FDA identified 776 such adulterated DSs, shockingly most of which were sexual enhancement products i.e. 353 (45.5%) of them. Predictably the most common pharmaceutical adulterant was sildenafil in these supplements i.e., 166 out of 353 products (47%)[181]. This adulteration is mainly owing to the fact that the dietary supplements do not pass through the pre-market approval by FDA unlike drugs and this needs priority attention keeping public health in mind.

Future of Natural aphrodisiacs: More Botanical drugs?

To date, there are only 2 FDA approved botanical drugs available as prescription drugs - sinecatechins, Veregen® and crofelemer, Mytesi™. Others like senna, psyllum and cascara are available as over-the-counter drugs [182]. In this context, there are at least 3 major problems that need to be addressed in order to derive more rational benefits from natural compounds.

- Plants that are traditionally considered 'block busters' lack scientific evidence on exact mode of action of the phytochemicals that accounts for the claimed results. To be specific, exact molecular target and its specificity need to be identified and proven
- Like drugs that are more than 98% pure in their chemical nature, natural substance need to be isolated and purified into a single chemical entity, with efficacy proven with this single chemical compound rather than working with whole extracts
- The singly extracted purest form of natural substance will have to undergo large set of carefully planned double blind clinical trials to evaluate safety, efficacy and toxicity.

It is undebatable that nutraceutical are gaining expanding popularity all over the world; but with questionable merits, given the fact that most of them enjoy the advantages of placebo effect. It is only a small fraction of consumers who report positive outcomes of treatment with dietary supplements. This will eventually bring down the confidence levels of consumers over the long run. In order to prevent this adverse situation, the researchers and clinical practitioners will have to take steps in all stages of research and clinical trials. Sexual dysfunction, especially erectile dysfunction is a commonly prevalent condition that affects people irrespective of race and region, hence setting the platform for pharma and nutraceutical companies to make business but with more rational and credible approach.

Future directions

In the context of sexual health problems, we majorly emphasize on three concerns for the future,

- In the context of gaining more scientific knowledge on the condition, it is important for individuals to address the health problem at right time. This will help both patients and also the clinicians, epidemiologists and research communities in understanding the etiology better and for development of drugs
- From the public health perspective, Nutraceutical and Pharma companies ought to be more responsible and ethical with their products and avoid chemical adulteration that can pose potential health hazards.
- It is the 'need of the hour' to give more rational approach towards traditional medicine. As is the case for drugs, more stringent clinical and efficacy studies for phytochemicals and other traditional medicines will have to be undertaken to fully harness the traditional knowledge acquired from centuries for the betterment of Human and animal lives.

References

1. RC Rosen. (2000) Prevalence and risk factors of sexual dysfunction in men and women., Curr. Psychiatry Rep. 189–195.
2. RO Rosen, WA Fisher, I Eardley, C Niederberger, A Nadel, M Sand. (2004) The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population, Curr. Med. Res. Opin. 607–617.
3. E Selvin, AL Burnett, EA Platz. (2007) Prevalence and Risk Factors for Erectile Dysfunction in the US, Am. J. Med. 120: 151–157.
4. RJ Levin. (2017) The Human Sexual Response Cycle, in: Textb. Clin. Sex. Med., Springer International Publishing. pp. 39–51.
5. IG Motofei, DL Rowland. (2005) The physiological basis of human sexual arousal: neuroendocrine sexual asymmetry, Int. J. Androl. 28 :78–87.
6. YC Wei, SR Wang, ZL Jiao, W Zhang, JK Lin, XY Li, SS Li, X Zhang, XH Xu. (2018) Medial preoptic area in mice is capable of mediating sexually dimorphic behaviors regardless of gender, Nat. Commun. 9:1–15.
7. JM Dominguez, EM Hull. (2005) Dopamine, the medial preoptic area, and male sexual behavior, Physiol. Behav. 86: 356–368.
8. EM Hull, JM Dominguez. (2006) Getting his act together: roles of glutamate, nitric oxide, and dopamine in the medial preoptic area. Brain Res. 1126: 66–75.
9. EM Hull, JW Muschamp, S Sato. (2004) Dopamine and serotonin: Influences on male sexual behavior, Physiol. Behav. 83: 291–307.
10. L Uphouse, J Guptarak. (2010) Serotonin and Sexual Behavior. pp. 347–365.
11. IF Ghalayini. (2004) Nitric oxide-cyclic GMP pathway with some emphasis on cavernosal contractility, Int. J. Impot. Res. 16 (2004) 459–469.
12. DF Mobley, M Khera, N Baum. (2017) Recent advances in the treatment of erectile dysfunction, Postgrad. Med. J. 93: 679–685.
13. FJ Luna-Vázquez, C Ibarra-Alvarado, A Rojas-Molina, I Rojas-Molina, MÁ Zavala-Sánchez,(2013) Vasodilator compounds

derived from plants and their mechanisms of action, Molecules. 18:5814–5857.

14. K Steinkamp-Fenske, L Bollinger, H Xu, Y Yao, S Horke, U Förstermann, H Li. (2007) Reciprocal regulation of endothelial nitric-oxide synthase and NADPH oxidase by betulinic acid in human endothelial cells, J. Pharmacol. Exp. Ther. 322: 836–842.

15. H Li, N Xia, I Brausch, Y Yao, U Förstermann. (2004) Flavonoids from artichoke (Cynara scolymus L.) up-regulate endothelial-type nitric-oxide synthase gene expression in human endothelial cells, J. Pharmacol. Exp. Ther. 310: 926–932.

16. K. Steinkamp-Fenske, L. Bollinger, N. Völler, H. Xu, Y. Yao, R. Bauer, U. Förstermann, H. Li, Ursolic acid from the Chinese herb Danshen (Salvia miltiorrhiza L.) upregulates eNOS and downregulates Nox4 expression in human endothelial cells, Atherosclerosis. 195 (2007).

17. N.F. Pavin, A.P. Izaguirry, M.B. Soares, C.C. Spiazzi, A.S.L. Mendez, F.G. Leivas, D. dos S. Brum, F.W.S. Cibin, Tribulus terrestris Protects against Male Reproductive Damage Induced by Cyclophosphamide in Mice, Oxid. Med. Cell. Longev. 2018 (2018).

18. H.J. Park, K.S. Lee, E.K. Lee, N.C. Park, Efficacy and Safety of a Mixed Extract of Trigonella foenum-graecum Seed and Lespedeza cuneata in the Treatment of Testosterone Deficiency Syndrome: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial , World J. Mens. Health. 36 (2018) 230.

19. M.I.B.M. Tambi, M.K. Imran, R.R. Henkel, Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism?, Andrologia. 44 (2012) 226–230.

20. S.-C. Tsai, Y.-C. Chiao, C.-C. Lu, P. Wang, Stimulation of the secretion of luteinizing hormone by ginsenoside-Rb1 in male rats, Chin. J. Physiol. 46 (2003) 1–7.

21. S. Lecomte, F. Demay, F. Ferrière, F. Pakdel, Phytochemicals targeting estrogen receptors: Beneficial rather than adverse effects?, Int. J. Mol. Sci. 18 (2017).

22. M.P. McCabe, I.D. Sharlip, R. Lewis, E. Atalla, R. Balon, A.D. Fisher, E. Laumann, S.W. Lee, R.T. Segraves, Incidence and Prevalence of Sexual Dysfunction in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015, J. Sex. Med. 13 (2016) 144–152.

23. E.O. Laumann, A. Paik, R.C. Rosen, Sexual dysfunction in the United States: Prevalence and predictors, J. Am. Med. Assoc. 281 (1999) 537–544.

24. C.B. Johannes, A.B. Araujo, H.A. Feldman, C.A. Derby, K.P. Kleinman, J.B. McKinlay, Incidence of erectile dysfunction in men 40 to 69 years old: Longitudinal results from the Massachusetts male aging study, J. Urol. 163 (2000) 460–463.

25. J.L. Shifren, B.U. Monz, P.A. Russo, A. Segreti, C.B. Johannes, Sexual problems and distress in united states women: Prevalence and correlates, Obstet. Gynecol. 112 (2008) 970–978.

26. M. Jaafarpour, A. Khani, J. Khajavikhan, Z. Suhrabi, Female Sexual Dysfunction: Prevalence and Risk Factors, J. Clin. DIAGNOSTIC Res. 7 (2013) 2877.

27. M.E. McCool, A. Zuelke, M.A. Theurich, H. Knuettel, C. Ricci, C. Apfelbacher, Prevalence of Female Sexual Dysfunction Among Premenopausal Women: A Systematic Review and Meta-Analysis of Observational Studies, Sex. Med. Rev. 4 (2016) 197–212.

28. J. Ma, L. Pan, Y. Lei, A. Zhang, Y. Kan, Prevalence of female sexual dysfunction in urban chinese women based on cutoff scores of the chinese version of the female sexual function index: A preliminary study, J. Sex. Med. 11 (2014) 909–919..

29. V. Mishra, S. Nanda, B. Vyas, R. Aggarwal, S. Choudhary, S. Saini, Prevalence of female sexual dysfunction among Indian fertile females, J. Midlife. Health. 7 (2016) 154–158.

30. V. Wekker, M.D.A. Karsten, R.C. Painter, C. van de Beek, H. Groen, B.W.J. Mol, A. Hoek, E. Laan, T.J. Roseboom, A lifestyle intervention improves sexual function of women with obesity and infertility: A 5 year follow-up of a RCT, PLoS One. 13 (2018) e0205934.

31. K. Esposito, M. Ciotola, F. Giugliano, M.I. Maiorino, R. Autorino, M. De Sio, G. Giugliano, G. Nicoletti, F. D'Andrea, D. Giugliano, Effects of intensive lifestyle changes on erectile dysfunction in men, J. Sex. Med. 6 (2009) 243–250.

32. WHO, Diabetes, WHO. (2018).

33. D. Jumani, O. Patil, Erectile dysfunction in diabetes mellitus: A review, J. Diabetol. 11 (2020) 1.

34. J.J. Cartledge, I. Eardley, J.F.B. Morrison, Advanced glycation end-products are responsible for the impairment of corpus cavernosal smooth muscle relaxation seen in diabetes, BJU Int. 87 (2001) 402–407.

35. P. Enzlin, C. Mathieu, A. Van Den Bruel, J. Bosteels, D. Vanderschueren, K. Demyttenaere, Sexual dysfunction in women with type 1 diabetes: A controlled study, Diabetes Care. 25 (2002) 672–677.

36. F. Elyasi, Z. Kashi, B. Tasfieh, A. Bahar, M. Khademloo, Sexual dysfunction in women with type 2 diabetes mellitus, Iran. J. Med. Sci. 40 (2015) 206–213.

37. A. Sai Ravi Shanker, B. Phanikrishna, C. Bhaktha Vatsala Reddy, Association between erectile dysfunction and coronary artery disease and it's severity, Indian Heart J. 65 (2013) 180–186.

38. P. Montorsi, P.M. Ravagnani, S. Galli, F. Rotatori, F. Veglia, A. Briganti, A. Salonia, F. Dehò, P. Rigatti, F. Montorsi, C. Fiorentini, Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial, Eur. Heart J. 27 (2006) 2632–2639.

39. C. Vlachopoulos, K. Rokkas, N. Ioakeimidis, C. Stefanadis, Inflammation, Metabolic Syndrome, Erectile Dysfunction, and Coronary Artery Disease: Common Links{A figure is presented}, Eur. Urol. 52 (2007) 1590–1600.

40. [40] T.M. Mills, K. Chitaley, R.W. Lewis, Vasoconstrictors in erectile physiology, Int. J. Impot. Res. 13 (2001) S29–S34.

41. L. Kriston, C. Günzler, A. Agyemang, J. Bengel, M.M. Berner, Effect of sexual function on health-related quality of life mediated by depressive symptoms in cardiac rehabilitation. Findings of the SPARK project in 493 patients, J. Sex. Med. 7 (2010) 2044–2055.

42. S.H. Hou, S. Grossman, M.E. Molitch, Hyperprolactinemia in Patients With Renal Insufficiency and Chronic Renal Failure Requiring Hemodialysis or Chronic Ambulatory Peritoneal Dialysis, Am. J. Kidney Dis. 6 (1985) 245–249.

43. S.B. Ahmed, S. Ramesh, Sex hormones in women with kidney disease, Nephrol. Dial. Transplant. 31 (2016) 1787–1795.

44. J. Buvat, Hyperprolactinemia and sexual function in men: A short review, Int. J. Impot. Res. 15 (2003) 373–377.

45. C.G. Bacon, M.A. Mittleman, I. Kawachi, E. Giovannucci, D.B. Glasser, E.B. Rimm, Sexual Function in Men Older Than 50 Years of Age: Results from the Health Professionals Follow-up Study, Ann. Intern. Med. 139 (2003).

46. E. Akkus, A. Kadioglu, A. Esen, S. Doran, A. Ergen, K. Anafarta, H. Hattat, Prevalence and correlates of erectile dysfunction in Turkey: A population-based study, Eur. Urol. 41 (2002) 298–304.

47. S.D. Navaneethan, M. Vecchio, D.W. Johnson, V. Saglimbene, G. Graziano, F. Pellegrini, G. Lucisano, J.C. Craig, M. Ruospo, G. Gentile, V.M. Manfreda, M. Querques, P. Stroumza, M. Torok, E. Celia, R. Gelfman, J.N. Ferrari, A. Bednarek-Skublewska, J. Dulawa, C. Bonifati, J. Hegbrant, C. Wollheim, E.A. Jannini, G.F.M. Strippoli, Prevalence and correlates of self-reported sexual dysfunction in CKD: A meta-analysis of observational studies, Am. J. Kidney Dis. 56 (2010) 670–685.

48. K. Park, I. Goldstein, C. Andry, M.B. Siroky, R.J. Krane, K.M. Azadzoi, Vasculogenic female sexual dysfunction: The hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency, Int. J. Impot. Res. 9 (1997) 27–37.

49. T. Nakahara, J. Narula, J.G.P. Tijssen, S. Agarwal, M.M. Chowdhury, P.A. Coughlin, M.R. Dweck, J.H.F. Rudd, M. Jinzaki, J. Mulhall, H.W. Strauss, 18 F-Fluoride Positron Emission Tomographic Imaging of Penile Arteries and Erectile Dysfunction, J. Am. Coll. Cardiol. 73 (2019) 1386–1394.

50. WHO, Hypertension, Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Hypertension. (2019).

51. F.A. Giuliano, A. Leriche, E.O. Jaudinot, A.S. De Gendre, Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both, Urology. 64 (2004) 1196–1201.

52. J. Jensen, The prevalence and etiology of impotence in 101 male hypertensive outpatients, Am. J. Hypertens. 12 (1999) 271–275.

53. K.R. Mitchell, C.H. Mercer, G.B. Ploubidis, K.G. Jones, J. Datta, N. Field, A.J. Copas, C. Tanton, B. Erens, P. Sonnenberg, S. Clifton, W. Macdowall, A. Phelps, A.M. Johnson, K. Wellings, Sexual function in Britain: Findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3), Lancet. 382 (2013) 1817–1829.

54. C.L. Hou, Y. Zang, R.C. Rosen, M.Y. Cai, Y. Li, F.J. Jia, Y.Q. Lin, G.S. Ungvari, C.H. Ng, H.F.K. Chiu, Y.T. Xiang, Sexual dysfunction and its impact on quality of life in Chinese patients with schizophrenia treated in primary care, Compr. Psychiatry. 65 (2016) 116–121.

55. E.W.Y. Harley, J. Boardman, T. Craig, Sexual problems in schizophrenia: Prevalence and characteristics. A cross sectional survey, Soc. Psychiatry Psychiatr. Epidemiol. 45 (2010) 759–766.

56. M. Olfson, T. Uttaro, W.H. Carson, E. Tafesse, Male sexual dysfunction and quality of life in schizophrenia, J. Clin. Psychiatry. 66 (2005) 331–338.

57. A. Serretti, A. Chiesa, Treatment-emergent sexual dysfunction related to antidepressants: A meta-analysis, J. Clin. Psychopharmacol. 29 (2009) 259–266.

58. D.K. Twitchell, D.A. Wittmann, J.M. Hotaling, A.W. Pastuszak, Psychological Impacts of Male Sexual Dysfunction in Pelvic Cancer Survivorship, Sex. Med. Rev. 7 (2019) 614–626.

59. L.R. Schover, M. van der Kaaij, E. van Dorst, C. Creutzberg, E. Huyghe, C.E. Kiserud, Sexual dysfunction and infertility as late effects of cancer treatment, Eur. J. Cancer, Suppl. 12 (2014) 41–53.

60. E.K. Abudu, S.A. Akanmu, O.O. Soriyan, A.A. Akinbami, A. Adediran, T.A. Adeyemo, C.C. Okany, Serum testosterone levels of HbSS (sickle cell disease) male subjects in Lagos, Nigeria, BMC Res. Notes. 4 (2011) 298.

61. A. Taddesse, I. Woldie, P. Khana, P.S. Swerdlow, J. Chu, J. Abrams, A. Abou-Samra, Hypogonadism in Men with Sickle Cell Disease (SCD): Benign Hematology Clinic, Detroit Medical Center, Detroit, MI, Blood. 118 (2011) 2132–2132.

62. A. Taddesse, I.L. Woldie, P. Khana, P.S. Swerdlow, J.W. Chu, J. Abrams, A.B. Abou-Samra, Hypogonadism in patients with sickle cell disease: Central or peripheral?, Acta Haematol. 128 (2012) 65–68.

63. M.R. Safarinejad, Evaluation of Semen Quality, Endocrine Profile and Hypothalamus-Pituitary-Testis Axis in Male Patients With Homozygous β-Thalassemia Major, J. Urol. 179 (2008) 2327–2332.

64. G. Petrakos, P. Andriopoulos, M. Tsironi, Pregnancy in women with thalassemia: Challenges and solutions, Int. J. Womens. Health. 8 (2016) 441–451.

65. E. Jorgenson, N. Matharu, M.R. Palmer, J. Yin, J. Shan, T.J. Hoffmann, K.K. Thai, X. Zhou, J.M. Hotaling, G.P. Jarvik, N. Ahituv, H. Wessells, S.K. Van Den Eeden, Genetic variation in the SIM1 locus is associated with erectile dysfunction , Proc. Natl. Acad. Sci. 115 (2018) 11018–11023.

66. M.L.E. Espir, J.W. Hall, J.G. Shirreffs, D.L. Stevens, Impotence in farm Workers Using Toxic Chemicals, Br. Med. J. 1 (1970) 423–425.

67. N. Vanova, J. Pejchal, D. Herman, A. Dlabkova, D. Jun, Oxidative stress in organophosphate poisoning: role of standard antidotal therapy, J. Appl. Toxicol. 38 (2018) 1058–1070.

68. X. Wu, X. Guo, H. Wang, S. Zhou, L. Li, X. Chen, G. Wang, J. Liu, H.S. Ge, R.S. Ge, A brief exposure to cadmium impairs Leydig cell regeneration in the adult rat testis, Sci. Rep. 7 (2017) 1–11.

69. V. Chauhan, S. Srikumar, S. Aamer, M.D. Pandareesh, A. Chauhan, Methylmercury exposure induces sexual dysfunction in male and female Drosophila melanogaster, Int. J. Environ. Res. Public Health. 14 (2017).

70. M. Ha, P. Zhang, L. Li, C. Liu, Triclosan Suppresses Testicular Steroidogenesis via the miR-6321/JNK/ Nur77 Cascade, Cell. Physiol. Biochem. 50 (2018) 2029–2045.

71. E.D. Lephart, K.D.R. Setchell, R.J. Handa, T.D. Lund, Behavioral effects of endocrine-disrupting substances: phytoestrogens., ILAR J. 45 (2004) 443–454.

72. C.M. Meston, B.B. Gorzalka, J.M. Wright, Inhibition of subjective and physiological sexual arousal in women by clonidine, Psychosom. Med. 59 (1997) 399–407.

73. R.H. Hodge, M.P. Harward, M.S. West, L. Krongaard-DeMong, M.B. Kowal-Neeley, Sexual function of women taking antihypertensive agents - A comparative study, J. Gen. Intern. Med. 6 (1991) 290–294.

74. R. Fogari, P. Preti, A. Zoppi, L. Corradi, C. Pasotti, A. Rinaldi, A. Mugellini, Effect of Valsartan and Atenolol on Sexual Behavior in Hypertensive Postmenopausal Women, Am. J. Hypertens. 17 (2004) 77–81.

75. P. CORVOL, A. MICHAUD, J. MENARD, M. FREIFELD, J. MAHOUDEAU, Antiandrogenic Effect of Spirolactones: Mechanism of Action, Endocrinology. 97 (1975) 52–58.

76. E. Jing, K. Straw-Wilson, Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review, Ment. Heal. Clin. 6 (2016) 191–196.

77. M. Philipp, R. Kohnen, O. Benkert, A comparison study of moclobemide and doxepin in major depression with special reference to effects on sexual dysfunction, Int. Clin. Psychopharmacol. 7 (1993) 149–154.

78. K.R. Kaufman, P.J. Struck, Gabapentin-induced sexual dysfunction, Epilepsy Behav. 21 (2011) 324–326.

79. F. Lotti, M. Maggi, Sexual dysfunction and male infertility, Nat. Rev. Urol. 15 (2018) 287–307.

80. R.S. Calabrò, G. Gervasi, A. Naro, R. de Luca, M. Marullo, P. Bramanti, Erectile Dysfunction in Individuals with Neurologic Disability: A Hospital-based Cross-sectional Study., Innov. Clin. Neurosci. 13 (2016) 10–4.

81. A.G. Tristano, The impact of rheumatic diseases on sexual function, Rheumatol. Int. 29 (2009) 853–860.

82. A. O'Toole, P.S. de Silva, L.G. Marc, C.A. Ulysse, M.A. Testa, A. Ting, A. Moss, J. Korzenik, S. Friedman, Sexual Dysfunction in Men With Inflammatory Bowel Disease: A New IBD-Specific Scale, Inflamm. Bowel Dis. 24 (2018) 310–316.

83. G. Duarte, H. Calmon, G. Radel, M. de F.P. de Oliveira, Psoriasis and sexual dysfunction: links, risks, and management challenges, Psoriasis Targets Ther. Volume 8 (2018) 93–99.

84. I. Simsek, G. Aslan, M. Akarsu, H. Koseoglu, A. Esen, Assessment of sexual functions in patients with chronic liver disease, Int. J. Impot. Res. 17 (2005) 343–345.

85. L.A. Brotto, The DSM diagnostic criteria for hypoactive sexual desire disorder in men, J. Sex. Med. 7 (2010) 2015–2030.

86. L.A. Brotto, The DSM diagnostic criteria for hypoactive sexual desire disorder in women, Arch. Sex. Behav. 39 (2010) 221–239.

87. A.H. Clayton, S.A. Kingsberg, I. Goldstein, Evaluation and Management of Hypoactive Sexual Desire Disorder, Sex. Med. 6 (2018) 59–74.

88. B.G.A. Stuckey, Female sexual function and dysfunction in the reproductive years: The influence of endogenous and exogenous sex hormones, J. Sex. Med. 5 (2008) 2282–2290.

89. T. Otani, Clinical review of ejaculatory dysfunction, Reprod. Med. Biol. 18 (2019) 331–343.

90. J.D. Xia, Y.F. Han, L.H. Zhou, Y. Chen, Y.T. Dai, Efficacy and safety of local anaesthetics for premature ejaculation: A systematic review and meta-analysis, Asian J. Androl. 15 (2013) 497–502.

91. S. Bangkok Hospital Medical Center, N. Bangkok Dusit Medical Services, L.O. Nicharojana, The Bangkok medical journal., 2016.

92. F. Giuliano, J. Allard, O. Rampin, S. Droupy, G. Benoit, L. Alexandre, J. Bernabe, Spinal proerectile effect of apomorphine in the anesthetized rat, in: Int. J. Impot. Res., Nature Publishing Group, 2001: pp. 110–115.

93. M.R. Melis, A. Argiolas, Central control of penile erection: A re-visitation of the role of oxytocin and its interaction with dopamine and glutamic acid in male rats, Neurosci. Biobehav. Rev. 35 (2011) 939–955.

94. M.R. Melis, R. Stancampiano, A. Argiolas, Hippocampal oxytocin mediates apomorphine-induced penile erection and yawning, Pharmacol. Biochem. Behav. 42 (1992) 61–66.

95. S. Succu, F. Sanna, C. Cocco, T. Melis, A. Boi, G.L. Ferri, A. Argiolas, M.R. Melis, Oxytocin induces penile erection when injected into the ventral tegmental area of male rats: Role of nitric oxide and cyclic GMP, Eur. J. Neurosci. 28 (2008) 813–821.

96. G. Bagdy, G.B. Makara, Paraventricular nucleus controls 5-HT2C receptor-mediated corticosterone and prolactin but not oxytocin and penile erection responses, Eur. J. Pharmacol. 275 (1995) 301–305.

97. J. Angulo, C. Peiró, C.F. Sanchez-Ferrer, S. Gabancho, P. Cuevas, S. Gupta, Ĩ.S. De Tejada, Differential effects of serotonin reuptake inhibitors on erectile responses, NO-production, and neuronal NO synthase expression in rat corpus cavernosum tissue, Br. J. Pharmacol. 134 (2001) 1190–1194.

98. M. Mas, Molecular mechanisms of penile erection., Arch. Esp. Urol. 63 (2010) 589–98.

99. J. V. Esplugues, NO as a signalling molecule in the nervous system, Br. J. Pharmacol. 135 (2002) 1079–1095.

100. Y.B. Choi, L. Tenneti, D.A. Le, J. Ortiz, G. Bai, H.S.V. Chen, S.A. Lipton, Molecular basis of NMDA receptor-coupled ion channel modulation by S- nitrosylation, Nat. Neurosci. 3 (2000) 15–21.

101. J.P. Kiss, E.S. Vizi, Nitric oxide: A novel link between synaptic and nonsynaptic transmission, Trends Neurosci. 24 (2001) 211–215.

102. C. Stief, F. Benard, R. Bosch, S. Aboseif, L. Nunes, T.F. Lue, E.A. Tanagho, Acetylcholine as a possible neurotransmitter in penile erection, J. Urol. 141 (1989) 1444–1448.

103. H.H. Knispel, C. Goessl, R. Beckmann, Basal and acetylcholine-stimulated nitric oxide formation mediates relaxation of rabbit cavernous smooth muscle, J. Urol. 146 (1991) 1429–1433.

104. W.G. Dail, R.W. Hamill, Parasympathetic nerves in penile erectile tissue of the rat contain choline acetyltransferase, Brain Res. 487 (1989) 165–170.

105. A. V. Vigdorchik, B.P. Parrish, G.A. Lagoda, J.A. McHenry, E.M. Hull, An NMDA antagonist in the MPOA impairs copulation and stimulus sensitization in male rats, Behav. Neurosci. 126 (2012) 186–195.

106. F. Giuliano, O. Rampin, K. Brown, F. Courtois, G. Benoit, A. Jardin, Stimulation of the medial preoptic area of the hypothalamus in the rat elicits increases in intracavernous pressure, Neurosci. Lett. 209 (1996) 1–4.

107. M.R. Zarrindast, H. Farahvash, Effects of GABA-ergic drugs on penile erection induced by apomorphine in rats, Psychopharmacology (Berl). 115 (1994) 249–253.

108. M.R. Melis, S. Succu, M.S. Mascia, A. Argiolas, The activation of γ aminobutyric acid A receptors in the paraventricular nucleus of the hypothalamus reduces non-contact penile erections in male rats, Neurosci. Lett. 314 (2001) 123–126.

109. A.D. Seftel, R.J. Mack, A.R. Secrest, T.M. Smith, Restorative Increases in Serum Testosterone Levels Are Significantly Correlated to Improvements in Sexual Functioning, J. Androl. 25 (2004) 963–972.

110. A. Aversa, A.M. Isidori, M.U. De Martino, M. Caprio, E. Fabbrini, M. Rocchietti-March, G. Frajese, A. Fabbri, Androgens and penile erection: Evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction, Clin. Endocrinol. (Oxf). 53 (2000) 517–522.

111. A. Aversa, A.M. Isidori, G. Spera, A. Lenzi, A. Fabbri, Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction, Clin. Endocrinol. (Oxf). 58 (2003) 632–638.

112. S.Y. Kalinchenko, G.I. Kozlov, N.P. Gontcharov, G. V. Katsiya, Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone, Aging Male. 6 (2003) 94–99.

113. C. Foresta, N. Caretta, M. Rossato, A. Garolla, A. Ferlin, Role of androgens in erectile function, J. Urol. 171 (2004) 2358–2362.

114. J.P. Mulhall, R. Valenzuela, N. Aviv, M. Parker, Effect of testosterone supplementation on sexual function in hypogonadal men with erectile dysfunction, Urology. 63 (2004) 348–352.

115. Z.J. Shen, X.L. Zhou, Y.L. Lu, Z.D. Chen, Effect of androgen deprivation on penile ultrastructure, Asian J. Androl. 5 (2003) 33–36.

116. A.M. Traish, K. Park, V. Dhir, N.N. Kim, R.B. Moreland, I. Goldstein, Effects of castration and androgen replacement on erectile function in a rabbit model, Endocrinology. 140 (1999) 1861–1868.

117. R. Singh, J.N. Artaza, W.E. Taylor, N.F. Gonzalez-Cadavid, S. Bhasin, Androgens Stimulate Myogenic Differentiation and Inhibit Adipogenesis in C3H 10T1/2 Pluripotent Cells through an Androgen Receptor-Mediated Pathway, Endocrinology. 144 (2003) 5081–5088.

118. A. Giraldi, A.H. Rellini, J. Pfaus, E. Laan, Female Sexual Arousal Disorders, J. Sex. Med. 10 (2013) 58–73.

119. I. Goldstein, Female sexual arousal disorder: New insights, Int. J. Impot. Res. 12 (2000) S152–S157.

120. L. Dennerstein, E.C. Dudley, J.L. Hopper, H. Burger, Sexuality, hormones and the menopausal transition, Maturitas. 26 (1997) 83–93.

121. Y. Meng, D.Y. Yang, K.M. Hebert, J.B. Savage, M. Alom, T.S. Kohler, L. Trost, What about the partner? —factors associated with patient-perceived partner dyspareunia in men with Peyronie's disease, Transl. Androl. Urol. 7 (2018) 935–940.

122. R.C. Webb, SMOOTH MUSCLE CONTRACTION AND RELAXATION, Adv. Physiol. Educ. 27 (2003) 201–206.

123. P. Clement, F. Giuliano, Anatomy and physiology of genital organs – men, Handb. Clin. Neurol. 130 (2015) 19–37.

124. T.M. Mills, R.W. Lewis, C.J. Wingard, A.E. Linder, L. Jin, R.C. Webb, Vasoconstriction, RhoA/Rho-kinase and the erectile response, Int. J. Impot. Res. 15 (2003) S20–S24.

125. A.W. Shindel, W.O. Brandt, D. Bochinski, A.J. Bella, T.F. Leu, Medical and Surgical Therapy of Erectile Dysfunction, MDText.com, Inc., 2000.

126. S.A. Huang, J.D. Lie, Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction, P T. 38 (2013) 407–419.

127. R. Tomsak, PDE5 inhibitors and permanent visual loss, Int. J. Impot. Res. 17 (2005) 547–549.

128. W. Liu, P.J. Antonelli, P. Dahm, T. Gerhard, J.A.C. Delaney, R. Segal, S. Crystal, A.G. Winterstein, Risk of sudden sensorineural hearing loss in adults using phosphodiesterase type 5 inhibitors: Population-based cohort study, Pharmacoepidemiol. Drug Saf. 27 (2018) 587–595.

129. H.M.T. Nguyen, A.T. Gabrielson, W.J.G. Hellstrom, Erectile Dysfunction in Young Men—A Review of the Prevalence and Risk Factors, Sex. Med. Rev. 5 (2017) 508–520.

130. S.M. Stahl, Mechanism of action of flibanserin, a multifunctional serotonin agonist and antagonist (MSAA), in hypoactive sexual desire disorder, CNS Spectr. 20 (2015) 1–6.

131. R. Baid, R. Agarwal, Flibanserin: A controversial drug for female hypoactive sexual desire disorder, Ind. Psychiatry J. 27 (2018) 154.

132. G. Rosse, Use of Bupropion in the Treatment of Sexual Dysfunction, ACS Med. Chem. Lett. 3 (2012) 786–786.

133. J.J. Shin, S.K. Kim, J.R. Lee, C.S. Suh, Ospemifene: A Novel Option for the Treatment of Vulvovaginal Atrophy, J. Menopausal Med. 23 (2017) 79.

134. M.C. Snabes, S.M. Simes, COMMENTARY: Approved Hormonal Treatments for HSDD: An Unmet Medical Need, J. Sex. Med. 6 (2009) 1846–1849.

135. W.H. Masters, V.E. Johnson, Human sexual inadequacy, Little, Brown, 1970.

136. P.J. Nobre, Treating Men's Erectile Problems, in: Wiley Handb. Sex Ther., John Wiley & Sons, Ltd, 2017: pp. 40–56.

137. T.Y. Rosenbaum, Physiotherapy treatment of sexual pain disorders, J. Sex Marital Ther. 31 (2005) 329–340.

138. S.A. Taha, M.W. Islam, A.M. Ageel, Effect of ambrein, a major constituent of ambergris, on masculine sexual behavior in rats., Arch. Int. Pharmacodyn. Ther. 329 (1995) 283–94.

139. P. Sandroni, Aphrodisiacs past and present: A historical review, Clin. Auton. Res. 11 (2001) 303–307.

140. S. Pandit, S. Biswas, U. Jana, R.K. De, S.C. Mukhopadhyay, T.K. Biswas, Clinical evaluation of purified Shilajit on testosterone levels in healthy volunteers, Andrologia. 48 (2016) 570–575.

141. R.M. Tyagi, U.M. Aswar, V. Mohan, S.L. Bodhankar, G.N. Zambare, P.A. Thakurdesai, Study of Furostenol Glycoside Fraction of Tribulus terresteris on Male Sexual Function in Rats, Pharm. Biol. 46 (2008) 191–198..

142. Y. Deole, B. Ashok, A. Thakar, S. Chavan, B. Ravishankar, H. Chandola, Evaluation of anti-depressant and anxiolytic activity of Rasayana Ghana Tablet (A compound Ayurvedic formulation) in albino mice, AYU (An Int. Q. J. Res. Ayurveda). 32 (2011) 375.

143. K.K. Shukla, A.A. Mahdi, M.K. Ahmad, S.N. Shankhwar, S. Rajender, S.P. Jaiswar, Mucuna pruriens improves male fertility by its action on the hypothalamus-pituitary-gonadal axis., Fertil. Steril. 92 (2009) 1934–40.

144. R.Y.K. Chan, W.F. Chen, A. Dong, D. Guo, M.S. Wong, Estrogen-like activity of ginsenoside Rg1 derived from Panax notoginseng, J. Clin. Endocrinol. Metab. 87 (2002) 3691–3695.

145. T.T. Hien, N.D. Kim, Y.R. Pokharel, S.J. Oh, M.Y. Lee, K.W. Kang, Ginsenoside Rg3 increases nitric oxide production via increases in phosphorylation and expression of endothelial nitric oxide synthase: Essential roles of estrogen receptor-dependent PI3-kinase and AMP-activated protein kinase, Toxicol. Appl. Pharmacol. 246 (2010) 171–183.

146. W.M. Yang, S.Y. Park, H.M. Kim, E.H. Park, S.K. Park, M.S. Chang, Effects of Panax ginseng on glial cell-derived neurotrophic factor (GDNF) expression and spermatogenesis in rats, Phyther. Res. 25 (2011) 308–311.

147. B.S. Low, S.B. Choi, H. Abdul Wahab, P. Kumar Das, K.L. Chan, Eurycomanone, the major quassinoid in Eurycoma longifolia root extract increases spermatogenesis by inhibiting the activity of phosphodiesterase and aromatase in steroidogenesis, J. Ethnopharmacol. 149 (2013) 201–207.

148. M.I.B.M. Tambi, M.K. Imran, R.R. Henkel, Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism?, Andrologia. 44 (2012) 226–230.

149. A. Maheshwari, N. Verma, A. Swaroop, M. Bagchi, H.G. Preuss, K. Tiwari, D. Bagchi, Efficacy of furosapTM, a novel trigonella foenum-graecum seed extract, in enhancing testosterone level and improving sperm profile in male volunteers, Int. J. Med. Sci. 14 (2017) 58–66.

150. J. Buffum, Pharmacosexology update: Yohimbine and sexual function, J. Psychoactive Drugs. 17 (1985) 131–132.

151. H.J. Vogt, P. Brandl, G. Kockott, J.R. Schmitz, M.H. Wiegand, J. Schadrack, M. Gierend, Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction, Int. J. Impot. Res. 9 (1997) 155–161.

152. A.A. Adeniyi, G.S. Brindley, J.P. Pryor, D.J. Ralph, Yohimbine in the treatment of orgasmic dysfunction, Asian J. Androl. 9 (2007) 403–407.

153. C.M. Meston, M. Worcel, The effects of yohimbine plus L-arginine glutamate on sexual arousal in postmenopausal women with sexual arousal disorder, Arch. Sex. Behav. 31 (2002) 323–332.

154. X. Chen, Cardiovascular protection by ginsenosides and ther Nitric oxide releasing action, Clin. Exp. Pharmacol. Physiol. 23 (1996) 728–732.

155. G. Salvati, G. Genovesi, L. Marcellini, P. Paolini, I. De Nuccio, M. Pepe, M. Re, Effects of Panax Ginseng C.A. Meyer saponins on male fertility., Panminerva Med. 38 (1996) 249–54.

156. K.J. Oh, M.J. Chae, H.S. Lee, H. Do Hong, K. Park, Effects of korean red ginseng on sexual arousal in menopausal women: Placebo-controlled, double-blind crossover clinical study, J. Sex. Med. 7 (2010) 1469–1477.

157. J. Park, H. Song, S.K. Kim, M.S. Lee, D.K. Rhee, Y.J. Lee, Effects of ginseng on two main sex steroid hormone receptors: Estrogen and androgen receptors, J. Ginseng Res. 41 (2017) 215–221.

158. J. Cho, W. Park, S. Lee, W. Ahn, Y. Lee, Ginsenoside-Rb1 from Panax ginseng C.A. Meyer activates estrogen receptor-α and -β, independent of ligand binding, J. Clin. Endocrinol. Metab. 89 (2004) 3510–3515.

159. S.A. Wani, P. Kumar, Fenugreek: A review on its nutraceutical properties and utilization in various food products, J. Saudi Soc. Agric. Sci. 17 (2018) 97–106.

160. Aradhana, A.R. Rao, R. Kale, Diosgenin—A growth stimulator of mammary gland of ovariectomized mouse, Indian J. Exp. Biol. 30 (1992) 367–370.

161. S. Sreeja, V.S. Anju, In vitro estrogenic activities of fenugreek Trigonella foenum graecum seeds., 2010.

162. E. Steels, A. Rao, L. Vitetta, Physiological Aspects of Male Libido Enhanced by Standardized Trigonella foenum-graecum Extract and Mineral Formulation, Phyther. Res. 25 (2011) n/a-n/a.

163. B.S. Low, P.K. Das, K.L. Chan, Standardized quassinoid-rich Eurycoma longifolia extract improved spermatogenesis and fertility in male rats via the hypothalamic-pituitary- gonadal axis, J. Ethnopharmacol. 145 (2013) 706–714.

164. B.S. Low, S.B. Choi, H. Abdul Wahab, P. Kumar Das, K.L. Chan, Eurycomanone, the major quassinoid in Eurycoma longifolia root extract increases spermatogenesis by inhibiting the activity of phosphodiesterase and aromatase in steroidogenesis, J. Ethnopharmacol. 149 (2013) 201–207.

165. S.M. Ezzat, M.M. Okba, M.I. Ezzat, N.M. Aborehab, S.O. Mohamed, Rho-Kinase II Inhibitory Potential of Eurycoma longifolia New Isolate for the Management of Erectile Dysfunction, Evidence-Based Complement. Altern. Med. 2019 (2019) 4341592.

166. L. Lampariello, A. Cortelazzo, R. Guerranti, C. Sticozzi, G. Valacchi, The magic velvet bean of mucuna pruriens, J. Tradit. Complement. Med. 2 (2012) 331–339.

167. K. Gauthaman, P.G. Adaikan, R.N.V. Prasad, Aphrodisiac properties of Tribulus Terrestris extract (Protodioscin) in normal and castrated rats, Life Sci. 71 (2002) 1385–1396.

168. K. Gauthaman, A.P. Ganesan, The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction - an evaluation using primates, rabbit and rat, Phytomedicine. 15 (2008) 44–54.

169. A. Adimoelja, P. Ganeshan Adaikan, Protodioscin from herbal plant Tribulus terrestris L improves the male sexual functions, probably via DHEA, 1997.

170. C.R.B. Gama, R. Lasmar, G.F. Gama, C.S. Abreu, C.P. Nunes, M. Geller, L. Oliveira, A. Santos, Clinical Assessment of Tribulus terrestris Extract in the Treatment of Female Sexual Dysfunction , Clin. Med. Insights Women's Heal. 7 (2014) CMWH.S17853.

171. A.W. Shindel, Z.C. Xin, G. Lin, T.M. Fandel, Y.C. Huang, L. Banie, B.N. Breyer, M.M. Garcia, C.S. Lin, T.F. Lue, Erectogenic and neurotrophic effects of icariin, a purified extract of horny goat weed (Epimedium spp.) in vitro and in vivo, J. Sex. Med. 7 (2010) 1518–1528.

172. M. Chen, J. Hao, Q. Yang, G. Li, Effects of icariin on reproductive functions in male rats, Molecules. 19 (2014) 9502–9514.

173. X. Chen, S. Salwinski, T.J.F. Lee, Extracts of Ginkgo biloba and ginsenosides exert cerebral vasorelaxation via a nitric oxide pathway, in: Clin. Exp. Pharmacol. Physiol., Blackwell Publishing, 1997: pp. 958–959.

174. A. Koltermann, A. Hartkorn, E. Koch, R. Fürst, A.M. Vollmar, S. Zahler, Ginkgo biloba extract EGb® 761 increases endothelial nitric oxide production in vitro and in vivo, Cell. Mol. Life Sci. 64 (2007) 1715–1722.

175. P.F. Smith, K. Maclennan, C.L. Darlington, The neuroprotective properties of the Ginkgo biloba leaf: A review of the possible relationship to platelet-activating factor (PAF), J. Ethnopharmacol. 50 (1996) 131–139.

176. Y. Wang, Y. Wang, B. McNeil, L.M. Harvey, Maca: An Andean crop with multi-pharmacological functions, Food Res. Int. 40 (2007) 783–792.

177. C. Carrasco-Gallardo, L. Guzmán, R.B. Maccioni, Shilajit: a natural phytocomplex with potential procognitive activity, Int. J. Alzheimers. Dis. 2012 (2012) 674142.

178. S. Kaur, P. Kumar, D. Kumar, M.D. Kharya, N. Singh, Parasympathomimetic effect of shilajit accounts for relaxation of rat corpus cavernosum., Am. J. Mens. Health. 7 (2013) 119–27.

179. S. Pandit, S. Biswas, U. Jana, R.K. De, S.C. Mukhopadhyay, T.K. Biswas, Clinical evaluation of purified Shilajit on testosterone levels in healthy volunteers, Andrologia. 48 (2016) 570–575.

180. A. Balasubramanian, N. Thirumavalavan, A. Srivatsav, J. Yu, J.M. Hotaling, L.I. Lipshultz, A.W. Pastuszak, An Analysis of Popular Online Erectile Dysfunction Supplements, J. Sex. Med. 16 (2019) 843–852.

181. J. Tucker, T. Fischer, L. Upjohn, D. Mazzera, M. Kumar, Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings, JAMA Netw. Open. 1 (2018) e183337.

182. US-FDA, What is a Botanical Drug? | FDA, (2017). https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/what-botanical-drug (accessed April 20, 2020).