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A COMPREHENSIVE REVIEW ON MEDICINAL PLANTS AND EMERGING THERAPIES FOR DIABETES INDUCED SEXUAL DYSFUNCTION

Abubakar Badeghar[1] and Prakash R. Biradar[2]*

[1]Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi-590010, Karnataka, India.

[2]Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi-590010, Karnataka, India.

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***Corresponding Author**
Prakash R. Biradar
Department of Pharmacology and Toxicology, KLE College of Pharmacy, Belagavi, KLE Academy of Higher Education and Research, Belagavi-590010, Karnataka, India.
prakashbiradar@klepharm.edu, prakashrb123@gmail.com

ABSTRACT

Diabetes mellitus, a chronic metabolic disorder, profoundly impacts reproductive health, contributing to complications such as sexual dysfunction. This review evaluates the efficacy of medicinal plants and emerging therapies in addressing diabetes-induced sexual dysfunction. Prominent botanicals, including *Tribulus terrestris*, *Withania somnifera*, and *Panax ginseng*, exhibit therapeutic potential by enhancing testosterone synthesis, mitigating oxidative stress, and improving vascular function. Rooted in traditional medicine, these plants offer complementary strategies to conventional pharmacological treatments. Beyond herbal interventions, the review highlights innovative approaches such as microbiome modulation, regenerative therapies using Human Urine-Derived Stem Cells (HUDSCs), and molecular interventions like pancreatic kininogenase to restore physiological balance. These multidisciplinary strategies aim to address the multifactorial pathogenesis of diabetes-related sexual dysfunction, encompassing hormonal deficits, endothelial damage, and neural impairment. By synthesizing current evidence, this review underscores the integrative potential of natural and novel therapies in improving reproductive outcomes for diabetic patients, advocating for further clinical validation to optimize safety and efficacy.

KEYWORDS: Diabetes mellitus, Sexual dysfunction, Medicinal plants, Regenerative medicine, Oxidative stress, Microbiome therapy.

INTRODUCTION

Diabetes mellitus is a prevalent chronic metabolic disorder that impacts the metabolism of carbohydrates, lipids, and proteins. Hyperglycaemia in diabetes is due to altered insulin secretion and/or resistance to insulin action. Elevated blood glucose levels can cause damage to the nervous system and blood vessels, leading to complications such as sexual dysfunction.[1] Reproductive dysfunction is one of the numerous complications of diabetes, affecting approximately 90% of diabetic patients.[2] In diabetic conditions, reproductive dysfunctions include testicular dysfunction, decreased fertility, reduced spermatogenesis, production of dysfunctional sperm, and retrograde ejaculation.[2] In addition, oxidative stress induced by hyperglycaemia is a significant contributing factor. Excessive reactive oxygen species (ROS) affect sperm DNA, sperm function, testicular metabolite levels, and the fusion events associated with fertilization, leading to infertility.[3] Administering currently available drugs for the treatment of sexual dysfunction in diabetic patients may interact with diabetes medications and alleviate complications.[3] Type 2 diabetes patients often receive various glucose-lowering drugs like sulphonylureas (e.g., glibenclamide, glyburide, glipizide, and gliclazide), which stimulate insulin secretion to reduce blood glucose levels.[4] Metformin, another antidiabetic medication, enhances insulin sensitivity to lower blood glucose levels.[4] Clomiphene citrate, a selective estrogen receptor modulator, can potentially enhance semen quality by promoting hormone synthesis and spermatogenesis.[5] Conversely, sildenafil, another medication, improves erectile function upon sexual arousal.[6] Transitioning to sulfonylureas was linked with higher risks of myocardial infarction, overall mortality, and severe hypoglycemia compared to patients staying on metformin.[7]Additionally, fertility drugs commonly cause side effects such as bloating, headaches, breast tenderness, upset stomach, hot flashes, and mood swings.[8] Medicinal plants have been essential in maintaining human health and improving quality of life for millennia. The practice of using plants as medicine is as ancient as human civilization itself. Currently, approximately 70% of the global population relies on herbal medicines, particularly in developing countries, due to their better cultural acceptability and compatibility with the human body. Many traditional medicinal systems, such as Ayurveda, Unani, homeopathy, naturopathy, Siddha, and other alternative medicine practices, have effectively utilized plants to treat various harmful diseases.[9] The integration of herbal medicines into treatment protocols offers a promising

avenue due to their efficacy and minimal side effects. Medicinal plants, such as *Tribulus terrestris*, *Withania somniferous*, and *Panax ginseng*, have shown potential in improving sexual function by enhancing testosterone levels, reducing oxidative stress, and improving blood flow. These herbs are part of traditional medicinal systems like Ayurveda and Unani, known for their holistic approach to treating various ailments, including sexual dysfunction. The therapeutic benefits of these plants stem from their bioactive compounds, which can address multiple pathways involved in diabetes-induced sexual dysfunction. Incorporating these herbal remedies could offer a complementary approach to conventional treatments, providing a more comprehensive management strategy for affected individuals.[10]

The modern treatment of diabetes-induced reproductive complications often comes with multiple side effects, such as an increased risk of stroke, heart attack, prostate tumorigenesis, and reduced spermatogenesis, particularly in hypogonadal patients receiving exogenous testosterone.[11] Due to these issues, there is a growing demand for new natural medications that have fewer side effects and can effectively target reproductive functions or structures impacted by diabetes.[11] Apart from the natural medications various other alternative therapies have also shown some beneficial effect in treating the diabetes induced sexual related dysfunction such as microbiomes, regenerative therapy and molecular therapy. Numerous studies have shown that plant extracts can improve male fertility in diabetic rats, primarily by enhancing glycemic control. Another promising therapeutic strategy is to directly address the reproductive pathways or parameters disrupted by diabetes using aphrodisiac plants that have minimal or no anti-hyperglycemic effects. These could be combined with plants that have antidiabetic properties to enhance their efficacy, ultimately aiming for a comprehensive restoration of reproductive functions altered by diabetes.[12]

In this review, we will discuss various medicinal plants and novel therapies that have shown promise in treating diabetes-induced sexual dysfunction. Plants such as *Tribulus terrestris*, *Withania somnifera*, and *Panax ginseng* will be highlighted for their potential benefits. These herbs can enhance testosterone levels, reduce oxidative stress, and improve blood flow, addressing multiple pathways involved in this condition. Additionally, the role of microbiomes, regenerative therapy and molecular therapy will be explored. By examining these plants and novel therapeutic approaches, we aim to provide a comprehensive overview of their therapeutic potential and application in the management of diabetes-induced sexual dysfunction.

Pathophysiology

Impact of diabetes on male fertility

Diabetes has been proven to negatively affect both male and female reproductive functions, contributing to a higher incidence of infertility. Approximately 90% of individuals with diabetes encounter disruptions in sexual function, including reduced libido, impotence, and infertility.[13] Diabetic men are particularly prone to various sexual issues, exacerbated by both advancing physical ailments and worsening psychological responses. Numerous studies have examined and documented the common pathologies faced by diabetic men, emphasizing the resulting reproductive impairments.[13]

Diabetes and Sexual dysfunction

Sexual dysfunction (SD) has been associated with the disease, the pathogenesis may involve vascular insufficiency and neuropathy, leading to ejaculation disorders and decreased libido.[14] Most research on male sexual dysfunction in diabetes focuses on erectile dysfunction, which occurs early and worsens with the disease's duration.

The Massachusetts Male Aging Study revealed that diabetic men are three times more likely to experience ejaculation dysfunction than non-diabetic men. Surveys indicate that 50-75% of diabetic men also report retrograde ejaculation, premature ejaculation,[15] reduced libido, and delayed sexual maturation. Chronic hyperglycemia in diabetes can significantly reduce libido, disrupt spermatogenesis,[16] and cause retrograde ejaculation or erectile dysfunction, decreasing sexual desire.

Animal studies show diabetic mice have longer mounting and intromission latencies but lower mounting and intromission frequencies. Although diabetes is a known risk factor for sexual dysfunction, it remains challenging to treat, and many aspects of its pathogenesis and treatment are still not well understood. The role of hyperglycemia, a key factor in diabetic vascular complications, in the development of sexual dysfunction is still unclear.[17]

Diabetic reproductive Injury and Hypothalamic pituitary testis axis

The male reproductive endocrine system is crucial for sperm maturation and normal sexual function. The hypothalamus regulates this system by producing Gonadotropin Releasing Hormone (GnRH), which stimulates the pituitary to release LH and FSH. These hormones then provide negative feedback to control further GnRH secretion. Recent studies have identified neuropeptide regulators of GnRH, with kisspeptin being essential for GnRH

pulsatility. Research by Jyothis et al. found that kisspeptin-10 significantly increased LH pulse frequency and secretion in men with type 2 diabetes, also boosting serum testosterone levels. Hormone levels of LH, FSH, and testosterone are markers of reproductive function, and disruptions in their balance can impair spermatogenesis and sexual function, potentially leading to infertility. Both clinical and research studies have shown that diabetes decreases serum LH and FSH levels. Testosterone, vital for spermatogenesis and libido, is produced by Leydig cells in the testes under LH stimulation.[18]

Diabetes and Endocrine hormone disorder

Sexual hormone regulation is a primary function of the testes and the male reproductive endocrine system, essential for normal reproductive function. In diabetic rats, a significant decrease in serum testosterone levels and in vitro testosterone secretion has been observed. Testosterone, produced by Leydig cells, is crucial for spermatogenesis and male libido. (Joan et al.) found that STZ-induced diabetes reduces Leydig cell numbers and impairs their function, suggesting that these changes lead to testosterone synthesis disorders, loss of libido, and decreased sexual capacity. However, testosterone replacement therapy did not fully reverse diabetes-induced sexual behaviour issues.[19]

Sertoli cells, which support germ cell development, are vital for spermatogenesis. Follicle Stimulating Hormone (FSH) plays a crucial role in germ cell maturation. In STZ-diabetic rats, a lack of insulin affected spermatogenesis by altering serum FSH levels rather than directly impacting the seminiferous epithelium.[20]

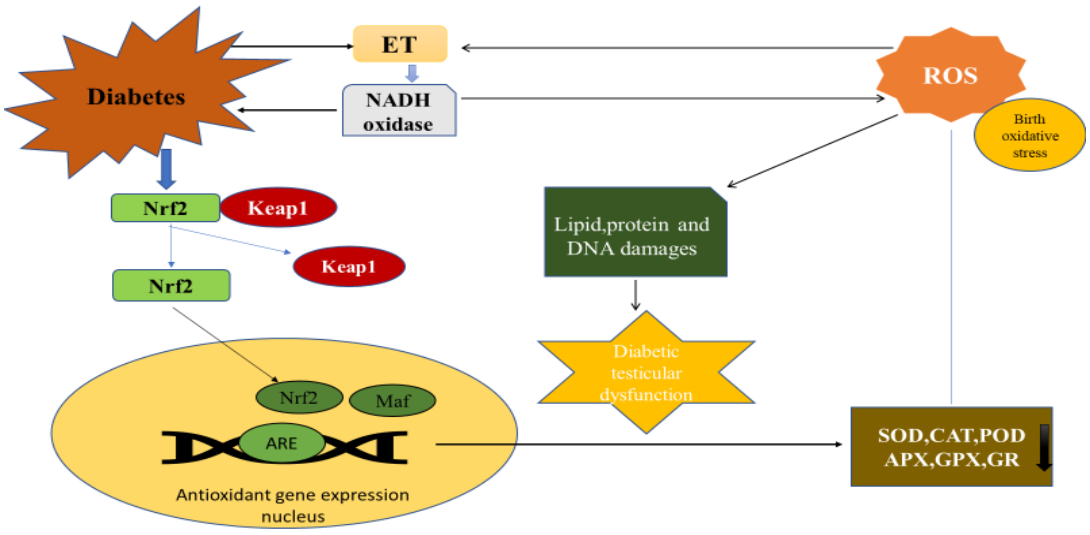
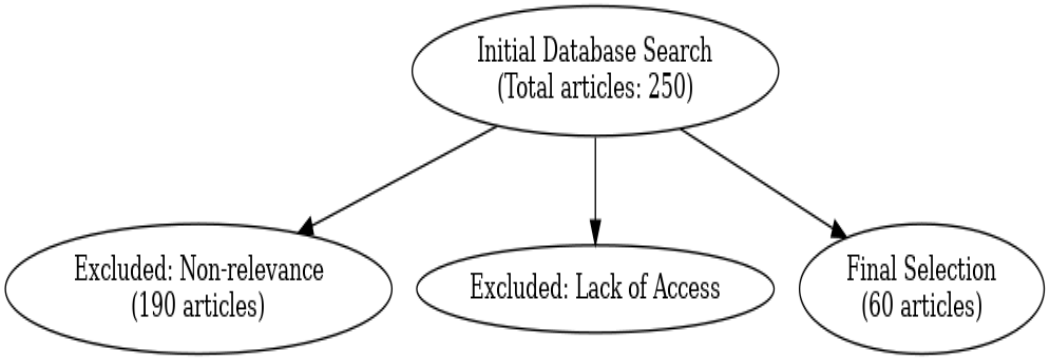


Fig 1: Schematic representation showing the diabetes mediated oxidative stress (mitochondrial dysfunction and ER stress) and the onset of diabetic reproductive

damages. ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; Nrf2: nuclear factor-erythroid2-related factor 2; ARE: antioxidant response element; ET: endothelin.

MATERIALS AND METHOD

A review of publications on diabetes and sexual dysfunction effective plants was conducted using databases such as Science Direct, PubMed, Wiley, Scopus, and Springer. The study employed keywords such as "medicinal plants," "diabetes," "sexual dysfunction," "symptom," "herbal," and "treatment." Out of 250 articles collected (published between 2005 and 2024), 190 were excluded due to either non-relevance or lack of access to the original articles.



1. **Initial database search**
   - Search terms: "medicinal plants," "diabetes," "sexual dysfunction," "symptom," "herbal," and "treatment."
   - Total articles found: 250

2. **Exclusion criteria**
   - Non-relevance: 190 articles excluded
   - Lack of access to original articles

3. **Final selection**
   - Relevant and accessible articles included in the review: 60

Dracaena arborea

Dracaena arborea, investigated for its effects on sexual dysfunction in type-1 diabetic rats, showed significant aphrodisiac properties. The aqueous and ethanol extracts increased mount and intromission frequencies and decreased latencies without significantly affecting blood

glucose levels. The observed effects are attributed to the antioxidant and androgenic properties of phenols, flavonoids, saponins, and sterols present in the extracts.[21]

Vitellaria paradoxa

Vitellaria paradoxa, commonly known as Shea butter tree, exhibits anti-diabetic properties through its various phytoconstituents such as triterpenes, steroids, and phenolics. The mechanisms of action include enhancement of insulin secretion, improvement of glucose uptake, and inhibition of carbohydrate metabolizing enzymes. These activities target pathways related to oxidative stress, inflammation, and glycemic control, making it beneficial for managing type 2 diabetes.[22]

Arctium lappa

Arctium lappa, or Burdock root, is used for its potential benefits in treating type 2 diabetes. The hydro-alcoholic extract of Burdock root was found to increase gonadotropins and testosterone levels while improving sperm count and viability in diabetic mice. The plant's active compounds, including lignans and flavonoids, contribute to its antioxidant and anti-inflammatory effects, targeting the endocrine system to regulate blood glucose levels.[23]

Albizia zygia

Albizia zygia has shown promising results in managing diabetes through its antioxidant and anti-inflammatory activities. The plant's extracts contain saponins, flavonoids, and tannins that help reduce oxidative stress and inflammation associated with diabetes. These phytoconstituents improve insulin sensitivity and modulate carbohydrate metabolism, making Albizia zygia an effective natural treatment for diabetes.[24]

Prangos ferulacea

Prangos ferulacea root extract demonstrates significant hypoglycaemic and hypolipidemic effects in diabetic rats. The hydro-alcoholic extract improves serum glucose and lipid profiles through its bioactive compounds such as coumarins and flavonoids. These compounds enhance insulin secretion, improve lipid metabolism, and reduce oxidative stress, contributing to the management of diabetes.[25]

Pupalia lappacea

Pupalia lappacea exhibits antidiabetic, antiadipogenic, and hypolipidemic activities both in vitro and in vivo. The plant's extracts contain flavonoids, saponins, and alkaloids, which

enhance insulin sensitivity, reduce blood glucose levels, and improve lipid profiles. The mechanisms include inhibition of carbohydrate metabolizing enzymes and enhancement of insulin secretion.[26]

Kaempferia parviflora

Kaempferia parviflora, known as black ginger, improves sexual performance and reduces diabetic complications in male rats. The plant's bioactive compounds, including polymethoxyflavones, exhibit antioxidant and anti-inflammatory properties, enhancing erectile function and insulin sensitivity. These effects help manage diabetes and its related sexual dysfunction.[27]

Scutellaria baicalensis

Scutellaria baicalensis, commonly known as Chinese skullcap, offers protective effects against type 2 diabetes-induced testicular damage. The plant's flavonoids, particularly baicalin and baicalein, reduce oxidative stress and modulate apoptosis-related genes, thereby preserving testicular function and improving fertility in diabetic rats.[28]

Gum Arabic (Acacia senegal)

Gum Arabic improves semen quality and reduces oxidative stress in diabetic rats. The plant's polysaccharides exhibit strong antioxidant properties, enhancing overall reproductive health and mitigating diabetes-induced damage. This makes Gum Arabic a beneficial supplement for managing diabetes and associated reproductive complications.[29]

Apocynin

Apocynin, derived from the plant *Apocynum cannabinum*, demonstrates antioxidant and anti-apoptotic effects in diabetic rats. It reduces oxidative stress and regulates apoptosis-related genes, thereby protecting testicular function and improving overall reproductive health. These properties make Apocynin a valuable natural compound for managing diabetes-induced reproductive damage.[30]

Tribulus terrestris

Tribulus terrestris enhances sexual function in diabetic conditions through its saponins, particularly protodioscin, which inhibit α-glucosidase and α-amylase, aiding in blood glucose regulation. The plant's flavonoids, such as quercetin, also contribute to its antihyperglycemic

effects. Studies show significant reductions in blood glucose levels and improved sexual function, making it a potential therapeutic agent for diabetes-induced sexual dysfunction.[31]

Panax ginseng

Panax ginseng exhibits its beneficial effects on diabetes-induced sexual dysfunction through its ginsenosides, which enhance nitric oxide production and improve penile erection. The antioxidant properties of ginseng reduce oxidative stress and improve endothelial function. This plant also modulates the release of insulin, contributing to better glucose regulation. Ginsenosides target various signalling pathways, such as the PI3K/Akt and MAPK pathways, to improve erectile function in diabetic conditions.[32]

Lycium chinense

Lycium chinense, commonly known as Chinese boxthorn, has significant antioxidative and antidiabetic properties beneficial for treating diabetes-induced sexual dysfunction. The root bark of this plant enhances spermatogenesis, increases antioxidant enzyme activities, and improves hormonal profiles in diabetic rats. Treatment with Lycium chinense notably decreases blood glucose levels and improves sperm quality and quantity. These effects are attributed to its rich content of bioactive compounds like flavonoids and phenolic glycosides.[33]

Withania somnifera

Withania somnifera (Ashwagandha) root extract shows potential in improving sexual function in diabetic male rats by significantly enhancing libido and sexual behaviour parameters. The key phytoconstituents include withanolides, sitoindosides, and various alkaloids. The mechanism of action involves the reduction of oxidative stress and modulation of sex hormone levels, contributing to improved erectile function and sperm quality.[34]

Butea frondosa

Butea frondosa (Flame of the Forest) bark extract exhibits significant improvement in sexual behaviour metrics such as mounting frequency and latency. The aqueous extract contains flavonoids, sterols, and glycosides which enhance sexual performance through the modulation of neurotransmitters and nitric oxide pathways.[35]

Eurycoma longifolia

Eurycoma longifolia (Tongkat Ali) demonstrates activating effects on male rats' sexual orientation towards females, indicating its potential to treat sexual dysfunction. The active constituents are eurycomanone, quassinoids, and alkaloids. These components work primarily by increasing testosterone levels and enhancing libido.[36]

Ferula hermonis

Ferula hermonis extract significantly stimulates sexual functions and libido in male rats. The methanolic extract contains sesquiterpene lactones and coumarins, which contribute to enhanced erectile function and sexual behaviour by modulating hormonal balance and reducing oxidative stress.[37]

Microdesmis keayana

Microdesmis keayana extract, rich in alkaloids, improves sexual function in male rats. The aqueous extract enhances sexual motivation and performance, potentially through central nervous system modulation and increased neurotransmitter activity.[38]

Turnera diffusa

Turnera diffusa (Damiana) aqueous extract aids in recovering sexual desire and motivation in sexually exhausted rats. Flavonoids are the main active constituents, which may influence the central nervous system to enhance sexual function.[39]

Chlorophytum borivilianum

Chlorophytum borivilianum (Safed Musli) root extract demonstrates significant improvement in sexual behavior in diabetic rats. The polysaccharide and saponin-rich aqueous extract reduces oxidative stress and enhances sexual functionality by increasing the weight of secondary sexual organs and improving sexual performance metrics.[40]

Gynura procumbens

Gynura Procumbens has been found to improve blood glucose levels, restore fertility, and libido in diabetic-induced male rats. It also mediates vasorelaxant activity. The plant contains antioxidant potential and has been reported to restore fertility and libido in diabetic-induced male rats.[41]

Curculigo orchioides

Curculigo Orchioides has been reported to have an effect on androgenic activity and sexual behavior. It contains phenolic compounds and saponins.[42]

Eucommia ulmoides Oliv

Eucommia ulmoides Oliv. leaf extract (EULE) protects endothelial function and improves hypothalamic-pituitary-gonadal (HPG) axis function in diabetic rats. It increases intracavernosal pressure, nitric oxide (NO) levels, and cyclic guanosine monophosphate (cGMP) concentrations while reducing oxidative stress by enhancing protein kinase B (Akt) and endothelial NO synthase (eNOS) activation. The phytoconstituents were identified through Ultra Performance Liquid Chromatography (UPLC). Targets involved include NO biosynthesis and HPG axis hormones (GnRH, FSH, LH, testosterone) and their receptors. EULE significantly improves erectile function in diabetic rats, suggesting its potential as a therapeutic option for diabetes-associated erectile dysfunction.[43]

Lecaniodiscus cupanioides

Lecaniodiscus cupanioides root extract improves sexual competence in paroxetine-induced sexually impaired rats. The extract contains alkaloids, anthraquinones, phenolics, saponins, and tannins. It reverses alterations in testicular function and boosts reproductive hormones like testosterone, FSH, and LH. It targets enzyme activities such as acid and alkaline phosphatases, lactate dehydrogenase, and gamma-glutamyl transferase, supporting its traditional use in managing male sexual disorders.[44]

Lepidium meyenii (Maca)

Lepidium meyenii, commonly known as maca, is shown to improve sexual function and libido in male rats by enhancing sperm production and motility. The plant's active compounds include macamides, macaenes, and glucosinolates, which are believed to regulate hormonal balance and improve reproductive health. Maca acts on the hypothalamic-pituitary-gonadal axis to increase testosterone levels and improve erectile function.[45]

Panax ginseng

Panax ginseng is traditionally used to treat sexual dysfunction. Its mechanisms involve improving NO synthesis and reducing oxidative stress in penile tissues. Ginsenosides, the primary active components, enhance erectile function by targeting endothelial cells and

smooth muscle relaxation. This plant also upregulates eNOS activity and promotes vascular health, essential for maintaining erectile function in diabetic conditions.[46]

Vaccinium myrtillus (Bilberry)

Vaccinium myrtillus, known as bilberry, shows promise in improving erectile dysfunction in diabetic rats through its rich anthocyanin content. These compounds enhance endothelial function and reduce oxidative stress, improving NO bioavailability. Bilberry targets vascular health and has been shown to alleviate symptoms of erectile dysfunction by supporting endothelial cell function and reducing inflammation.[47]

Sanrego (Lunasia amara)

Sanrego (Lunasia amara) enhances sexual function by influencing androgenic activity and increasing blood flow. The plant contains alkaloids, flavonoids, and saponins, targeting androgen receptors and vascular endothelium. Traditionally used in South Sulawesi as an aphrodisiac, it effectively improves sexual function in diabetic rats induced by a high-fat diet.[48]

Human Urine-Derived Stem Cells (HUDSCs)

HUDSCs improve erectile function by enhancing endothelial function and increasing angiogenesis, primarily through the action of fibroblast growth factor 2 (FGF2). This treatment has shown effectiveness in improving erectile function in type 2 diabetic rats.[49]

Pancreatic kininogenase

Pancreatic kininogenase enhances erectile function through vasodilation and anti-inflammatory effects by targeting kinin receptors. It has proven effective in streptozotocin-induced type 2 diabetic rats.[50]

Curcumin

Curcumin, with its curcuminoids, acts as an antioxidant and anti-inflammatory agent, improving endothelial function. It targets the NF-κB and Nrf2 pathways, reducing oxidative stress and improving erectile function in diabetic rats.[51]

Momordica charantia

Momordica charantia (MC) improves sexual function in diabetic rats by reducing blood glucose levels, enhancing testicular antioxidant enzymes, and reducing testicular apoptosis. It contains flavonoids, polysaccharides, saponins, phenolic compounds, triterpenoids, alkaloids,

and sterols. Targets include blood glucose, HbA1c, insulin, testosterone, FSH, LH, and testicular antioxidant enzymes. MC significantly reduces blood glucose and HbA1c levels, increases insulin and testosterone levels, improves histopathological changes in testes, and decreases spermatogenic cell apoptosis.[52]

Gross Saponins of Tribulus terrestris (GSTT)

Gross saponins of Tribulus terrestris (GSTT) protect against diabetes-induced erectile dysfunction by improving penile endothelial function, inhibiting cavernosum fibrosis, and preventing apoptosis. They enhance nitric oxide production, reduce oxidative stress, and inhibit glycolipid metabolism disorders. GSTT synergizes with sildenafil to improve erectile function in diabetic models.[53]

Gongronema latifolium

Gongronema latifolium enhances sexual health and libido by significantly increasing serum testosterone, FSH, and LH levels while decreasing progesterone levels. The ethanol leaf extract contains alkaloids, saponins, flavonoids, steroids, triterpenoids, tannins, and glycosides. These phytoconstituents target hormonal pathways, crucial for managing erectile dysfunction and overall sexual function. This plant's extract shows potential in improving male reproductive hormones and treating erectile dysfunction.[54]

Urtica dioica L. (Urticaceae)

Urtica dioica, or stinging nettle, protects against histopathological and morphometric alterations in the seminiferous tubules of diabetic rats. Its hydroalcoholic extract enhances the diameter and epithelial height of seminiferous tubules, counteracting diabetes-induced reductions. The plant contains phenolic and flavonoid compounds with strong antioxidant properties, targeting oxidative stress and improving the structure of seminiferous tubules in diabetic rats.[55]

Allium ascalonicum (Liliaceae)

Allium ascalonicum, commonly known as shallot, has shown promising effects in managing diabetes-induced sexual dysfunction. The bulb juice of this plant, when administered to diabetic mice, significantly decreases blood glucose levels and enhances testicular function. This includes increased gonadal index, sperm count, motility, and viability, while reducing abnormal sperm counts. These beneficial effects are attributed to its antioxidant properties, particularly quercetin, which helps mitigate oxidative stress-induced testicular damage.[56]

Allium cepa (Liliaceae)

The bulb juice of *Allium cepa*, or onion, has demonstrated potential in improving reproductive health in diabetic rats. Regular administration significantly increases epididymal sperm count and the percentage of viable and motile sperm. This suggests that Allium cepa may help counteract the adverse reproductive effects associated with diabetes, enhancing overall sperm quality and viability.[57]

Allium sativum (Liliaceae)

Commonly known as garlic, Allium sativum has been studied for its impact on reproductive complications of diabetes. Research indicates that garlic administration can significantly improve sperm count, motility, and overall reproductive health in diabetic male rats. These effects are primarily due to its antioxidant properties, which protect against oxidative stress and support reproductive function.[58]

Amaranthus spinosus (Amaranthaceae)

Amaranthus spinosus, or spiny amaranth, is noted for its antidiabetic, antihyperlipidemic, and spermatogenic effects. In diabetic rats, it not only lowers blood glucose levels but also improves sperm count and motility. This plant's efficacy in enhancing reproductive health is linked to its ability to manage blood glucose and lipid levels, thereby supporting overall sexual health in diabetes.[59]

Asparagus racemosus (Asparagaceae)

Asparagus racemosus, known as Shatavari, is traditionally used for its reproductive health benefits. In diabetic male rats, it has shown significant improvements in sexual function, including increased libido and sperm count. The plant's effects are attributed to its antioxidant properties, which help mitigate oxidative damage and support reproductive function in diabetic conditions.(60]

Coccinia indica

Coccinia indica is known for its hypoglycemic effects, which help in the management of diabetes. It protects testicular tissues by reducing oxidative stress and lipid peroxidation, thereby ameliorating testicular dysfunction and improving sperm quality in diabetic rats.[61]

Eugenia jambolana

Eugenia jambolana has shown to improve testicular function in diabetic conditions by modulating genomic and proteomic expressions. Its antioxidative properties play a significant role in mitigating oxidative stress-induced testicular damage.[62]

Ficus benghalensis

Ficus benghalensis has been found to improve sperm quality, LDH-C4 activity, and testosterone levels in diabetic rats. Its protective effects on testicular functions are attributed to its antioxidative properties.[63]

Cnidoscolus aconitifolius (Euphorbiaceae)

An ethanolic extract of Cnidoscolus aconitifolius leaves was administered orally to ALX-induced diabetic rats at doses of 100, 500, and 1000 mg/kg body weight per day for 4 weeks. The treatment significantly improved caudal epididymal sperm count, motility, and live/dead ratio, although it did not affect sperm structural abnormalities.[64]

Cocculus hirsutus (Menispermaceae)

A methanolic extract of *Cocculus hirsutus* aerial parts was given to STZ-induced diabetic rats at doses of 400 and 800 mg/kg body weight per day for 15 days. The extract significantly decreased blood glucose levels and increased insulin secretion. Additionally, it increased the weight of reproductive organs, cauda epididymal sperm count, motility, and testosterone levels in both testes and serum, and it resumed spermatogenesis in seminiferous tubules, likely due to its insulogenic and androgenic activity.[65]

Danae racemosa (Ruscaceae)

An aqueous extract of *Danae racemosa* was given orally to STZ-induced diabetic rats at a dose of 400 mg/kg body weight per day for 28 days. The treatment resulted in increased serum testosterone and testes weight compared to diabetic control rats, likely due to reduced ROS production.[66]

Urtica pilulifera (Urticaceae)

Administered at doses of 1.0 and 2.0 g/kg body weight per day orally for 4 weeks to STZ-induced diabetic rats, this extract significantly decreased serum glucose levels and increased testosterone levels in both serum and testis, improving sperm count and motility. The effects

are attributed to the antioxidant activities of bioactive compounds in the extract, which may reverse the toxic action of STZ, restoring β-cell integrity and metabolic function.[67]

Vernonia amygdalina (Asteraceae)

Administered at 200 mg/kg body weight per day orally for 28 days to STZ-induced diabetic rats, this extract showed slight improvement in the histoarchitecture of the testes, with the presence of few Sertoli and spermatogenic cells, despite some vacuoles in seminiferous tubules. The improvements are likely due to the antioxidant activity of the extract.[68]

Hibiscus sabdariffa (Malvaceae)

Administered at 100 mg/kg body weight per day orally for 28 days to STZ-induced diabetic rats, this extract significantly lowered fasting blood glucose levels and increased plasma insulin levels. It also increased reproductive organ weights, epididymal sperm count, sperm motility, and plasma levels of FSH, while reducing sperm abnormalities. These effects are attributed to the extract's free radical scavenging properties.[69]

Ligustrum lucidum (Oleaceae) Fruits

Administered at 30 g/kg per day by gavage for 110 days to STZ-induced diabetic rats, this extract increased serum levels of LH, FSH, and testosterone. It counteracted the damaging effect of diabetes on spermatogenesis, demonstrating its potential in improving reproductive health in diabetic conditions.[70]

Mucuna pruriens (Leguminaceae)

Administered at 200 mg/kg body weight per day orally for 60 days to STZ-induced diabetic rats, this extract significantly decreased blood glucose levels. It also increased serum levels of FSH, LH, and testosterone, improving sexual behaviour, libido, potency, and sperm parameters. The effects are likely due to the extract's phytoconstituents and their antioxidative and androgenic properties.[71]

Musa paradisiaca (Musaceae)

Administered at 200 mg/kg body weight twice a day orally for 28 days to STZ-induced diabetic rats, this extract significantly decreased fasting blood glucose and HbA1c levels and increased insulin levels. It increased reproductive organ indices, epididymal sperm count, sperm motility, serum testosterone level, and testicular cholesterol level. The extract also corrected oxidative stress markers and pro-apoptotic mRNA expression, indicating

antihyperglycemic and antioxidative activity for treating diabetes-induced reproductive disorders.[72]

Nigella sativa (Ranunculaceae)

Administered at 200 mg/kg of diet mixed in the diet to ALX-induced diabetic rats, this treatment significantly decreased plasma glucose levels. It also increased reproductive organ weights, improved semen quantity and mobility, serum testosterone levels, and activities of antioxidant enzymes in reproductive organs. These effects may be due to the antioxidant and androgenic effects of its phytoconstituents.[73]

Ocimum gratissimum (Lamiaceae)

Administered at 200 mg/kg body weight per day orally for 28 days to STZ-induced diabetic rats, this extract significantly improved the seminiferous tubules, with numerous boundary and Sertoli cells present in their lining epithelium. The protective effects are likely due to the high levels of alkaloids, flavonoids, and tannins found in the extract.[74]

Pseudocedrela kotschyi root

Administered at 250 and 500 mg/kg body weight per day orally for 4 weeks to ALX-induced diabetic rats, this extract significantly decreased plasma glucose levels. It increased the body, testes, and epididymis weights, serum testosterone levels, sperm count and motility, and testicular GSH, CAT, SOD, and GPx levels, while decreasing MDA levels. These effects suggest the extract's antioxidative properties.[75]

Sesamum indicum (Pedaliacae) Seeds

Administered at 100 mg/kg body weight per day intraperitoneally for 6 weeks to STZ-induced diabetic rats, this extract significantly decreased blood glucose levels. It increased serum levels of FSH, LH, and testosterone, and improved testicular tissue damage by protecting spermatogenic and Sertoli cells while decreasing cell apoptosis. These effects might be due to the extract's protective effect against oxidative stress-induced impaired testicular functions.[76]

Anacyclus pyrethrum (Aqarqarha) DC

Used in Unani medicine for its various therapeutic properties, including spermatogenic, anti-diabetic, and anticancer activities, the petroleum ether extract of *Anacyclus pyrethrum* root enhances sexual potential, increasing penile erection index and reducing mount and

intromission latency periods. The aqueous extract increases body and sex organ weights, sperm count, and reduces abnormal spermatozoids.[77]

Citrullus vulgaris (Tarbooz) SCHRAD

Naturally containing L-citrulline, this compound releases nitric oxide (NO), increasing blood flow, including to the penis, thus aiding in the treatment of diabetes-induced erectile dysfunction (DIED). L-citrulline's structural resemblance to arginine helps mitigate diabetic complications by enhancing NO-mediated vasodilation.[78]

Commiphora mukul (Muquil) (Burseraceae)

Known for its anti-diabetic activity, *Commiphora mukul* acts as a dual activator for PPAR-α and PPAR-γ. Its active principle, guggulsterone, exhibits hypoglycemic and hypolipidemic effects, beneficial for type II diabetes. By activating the farnesoid X receptor, which regulates lipid and glucose homeostasis and influences endothelial function and atherosclerosis, it is proposed to help treat diabetes-induced erectile dysfunction (DIED) by restoring endothelium-dependent relaxation in cavernous tissue.[79]

Asparagus adscendens (Musli Siyah) ROXB. (Asparagaceae)

Found in the Western Himalayas, this plant's tubers are known for their demulcent, nutritive, and aphrodisiac properties. They contain steroidal saponins like stigmasterol and sarsapogenin, which may reduce seminal weakness and cure impotence. Additionally, the active constituents have insulinotropic effects, enhancing glucose uptake in adipocytes and inhibiting starch digestion, beneficial for diabetes management.[80]

Myristica fragrans (Bisbasa) HOUTT. (Myristicaceae)

Bisbasa seeds, known for their stimulant and hallucinogenic properties, contain compounds that prolong the actions of other ingredients and enhance the release of L-DOPA due to β-phenethylamines and ephedrine. Ascribed with rasayana (rejuvenative) properties in Ayurvedic texts, their antioxidant potential might aid in treating diabetes-induced erectile dysfunction by mitigating oxidative stress.[81]

Microbiomes involved in T2DM

Research indicates that changes in the gut microbiome are linked to the development of type 2 diabetes mellitus (T2DM). Key findings include decreased microbial diversity, reduced **Firmicutes** (including **Clostridium species**), and increased **Proteobacteria**, which correlate

with elevated plasma glucose levels. Additionally, butyrate-producing bacteria (e.g., **Faecalibacterium prausnitzii** and **Roseburia spp**.) are often diminished in T2DM, while Lactobacillus species may increase. Some studies also report decreased **Akkermansia muciniphila**, which is associated with host adiposity regulation. These alterations suggest a significant role of the gut microbiome in insulin sensitivity and glucose metabolism, though causal relationships need further investigation.[82]

Microbiomes involved in Sexual dysfunction

Research indicates that specific gut microbiomes are involved in sexual dysfunction, particularly erectile dysfunction (ED). Clostridium XVIII is associated with intestinal disorders and ED, while **Alistipes** may inhibit inflammatory factors like TNF-α, with lower levels linked to cardiovascular risks. **Allobaculum**, Bifidobacterium**, Eubacterium**, and **Anaerotruncus** are reduced in diabetic mouse models of ED, alongside increased TMAO and LPS levels, which promote vascular inflammation and contribute to ED. These findings suggest that gut microbiome alterations may play a significant role in the development and progression of ED.[83]

Vascular regenerative therapy

Vascular regenerative approaches, show promise in treating diabetes-induced sexual dysfunction by repairing and regenerating damaged vascular tissues. Mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) play a crucial role in this process, promoting tissue repair through differentiation and secretion of growth factors. Gene therapy targeting endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF) enhances nitric oxide production and neovascularization, improving blood flow. Additionally, PDE5 inhibitors support these regenerative processes by mobilizing EPCs. These innovative therapies address the underlying vascular issues, offering effective treatment options for diabetes-induced sexual dysfunction.[84]

Adipose-derived stem cells (ASCs)

Adipose-derived stem cells (ASCs) have shown promising therapeutic potential in treating diabetes-induced erectile dysfunction (DMED). ASCs promote endothelial function, vascularization, and smooth muscle regeneration in the corpus cavernosum, which is crucial for penile erection. They also inhibit fibrosis, reduce inflammation, and improve neuralization, all of which contribute to enhanced erectile function. Animal studies have

demonstrated the efficacy of ASCs in restoring erectile function, though clinical application in humans still requires further research to establish safety and effectiveness.[85]

CONCLUSION

The review highlights the significant potential of medicinal plants and novel therapies in managing diabetes-induced sexual dysfunction. Plants such as *Tribulus terrestris*, *Withania somnifera*, and Panax ginseng exhibit mechanisms that enhance testosterone levels, reduce oxidative stress, and improve blood flow, addressing multiple pathways involved in this condition. Additionally, regenerative therapies like HUDSCs and molecular therapies like pancreatic kininogenase offer promising avenues for treatment by improving endothelial function and promoting angiogenesis. Integrating these herbal remedies and novel therapies with conventional treatments could provide a more comprehensive and effective management strategy for individuals affected by diabetes-induced sexual dysfunction. The findings underscore the importance of further research to validate these therapeutic approaches and explore their full potential in clinical applications.

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