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REVIEW

Therapeutic Challenges of Diabetes Mellitus-Related Erectile Dysfunction and The Potential Therapeutic Role of Medicinal Plants: A Narrative Review

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Abstract: Erectile dysfunction (ED) is a common male sexual dysfunction and can be induced by diabetes mellitus (DM). Diabetes mellitus-induced erectile dysfunction (DMED) affects various aspects of the patient's quality of life, mental well-being, and relationship dynamics. Given the increasing incidence of DM worldwide, the incidence of DMED is expected to increase accordingly. There are more challenges to treat DMED compared to non-DMED. The efficacy of oral phosphodiesterase-5 inhibitors is often ineffective in DMED and there is a need to search for effective drugs. Medicinal plants such as Eucommia ulmoides Oliv. Leaf, Cordycep militaris have been used in treating DMED in some experiments. And some ingredients from the medicinal plants such as Icariside II, Panax notoginseng Saponins have also shown to be beneficial in improving erectile function in animal models of DMED. These medicinal plants and ingredients may act by regulating hormone levels, ameliorating oxidative damage, and promoting NO/cGMP. We summarize the challenges in treating DMED due to related complicated pathogenesis and limited therapeutic options, while particularly highlight the role of the medicinal plants and their ingredients in DMED.
Keywords: erectile dysfunction, diabetes mellitus, medicinal plant, mechanism, treatment

Introduction

Erectile dysfunction (ED) is the inability to obtain or maintain sufficient penile erection to complete a satisfactory sexual life,[1] which seriously affects patients' physical and mental health, quality of life and relationship dynamics. Audiovisual Sexual Stimulation, Nocturnal Penile Tumescence and Rigidity, and Intracavern osal Injection combined with Color Doppler Duplex Ultrasonography are the main methods to diagnose ED.[1] And many factors can induce ED such as diabetes mellitus (DM), psychosomatic factors, ageing, dietary factors, neurogenic causes, etc. Among them, ED is one of the most common complications in DM patients and is closely affected by the severity and duration of DM and glycaemic control.[2,3] Studies have shown that people with DM are 3.5 times more likely to have ED compared to healthy men, with approximately 37.5% in type 1 DM and 66.3% in type 2 DM suffering from ED.[4] Additionally, the prevalence of diabetes mellitus-induced erectile dysfunction (DMED) positively correlated with increasing age, with 26.5% among DM patients under 40 years and rising to 91% in those over 70.[5] DMED patients have poorer erectile function and sexual satisfaction compared to non- DMED.[6] The development of DMED is a complex, multifactorial process involving vascular endothelial dysfunction, neuropathy, abnormal hormone levels, and psychological disorders.[7] Oral phosphodiesterase-5 (PDE5) inhibitor is recommended as the first-line therapy to improve penile erections.[8,9] However, the therapeutic mechanism of ED depends on the integrity of the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway, and on-demand PDE5 inhibitors have an overall efficacy of 60–70% for ED; meaning 30–35% of patients fail to respond to the PDE5 inhibitor.[10] Of these drug-refractory ED patients, DMED is one of the main reasons.[6] As the total number of patients with DMED increases, it is important to explore new and novel treatment strategies.

In recent years, studies have shown that medicinal plants can treat various diseases by modulating relevant signalling pathways, attenuating oxidative stress, inhibiting inflammatory responses, and regulating programmed cell death, with

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the advantages of multi-pathway, and multi-targeting.[11–13] They have demonstrated positive effects on various conditions in urology, reproduction, and sexual medicine.[14–16] In this narrative review, we summarize the mechanisms of DMED and its current treatment challenge and focus on the research progress in medicinal plants and their active ingredients, while aiming to provide new treatment strategies and incorporating complementary and alternative therapies for DMED.

Multiple Factors of DMED

After receiving the erection signal from the hypothalamic center, the penile cavernous nerve releases neuronal nitric oxide synthase (nNOS) with the corpus cavernosum (CC) stimulates the synthesis and release of endothelial nitric oxide synthase (eNOS). Both nNOS and eNOS are responsible for the nitric oxide (NO), which acts on the guanylate cyclase in the corpus cavernosum smooth muscle cells (CCSMC) to convert it into cyclic guanosine monophosphate (cGMP),[17] resulting in a series of biochemical pathways responsible for penile erection.[17] The pathological changes induced by the DM on the CC are complex, such as nerve damage, vascular dysfunction, endothelial cell dysfunction, decreased smooth muscle diastolic capacity, and cavernous fibrosis.[4]

Vascular dysfunction in DM patients can be related to underlying penile arteriosclerosis stenosis and micro-arterial occlusion, which leads to penile arterial hypertension and cavernous arterial insufficiency.[18,19] Microangiopathy induced by DM can also disrupt the ability of the venous plexus in the CC to close.[20] In a cross-sectional study of 87 DMED participants, penile vasculopathy was found in 21.8% (17.2% had arterial insufficiency, 2.3% had a venous leak, and 2.3% had arterial insufficiency with a venous leak).[21] The mechanism by which DM induces vascular structural lesions may be related to the massive production of advanced glycosylation end products (AGEs) in the penile vasculature. AGEs can bond covalently with vascular collagen, increasing vascular permeability and endothelial adhesion molecule expression, which leads to vascular pathology.[22] AGEs can also affect DNA transcription and replication, leading to changes in intracellular proteins that contribute to atherosclerosis and the narrowing of penile artery lumens.[23]

The hyperglycemic state not only induces abnormal endothelial cell function by reducing the expression of vascular endothelial growth factor (VEGF), a key regulator of endothelial cell proliferation, angiogenesis, and anti-apoptosis,[24,25] but also elevates reactive oxygen species (ROS) levels, consequently diminishing NO activity.[26,27] Additionally, persistent endothelial dysfunction and significant injury to the cavernosal vascular bed can also lead to endothelial cell apoptosis.[28] Hyperglycemia significantly reduces the expression of smooth muscle gap junction proteins and the permeability of their derived gap junctions,[29,30] affecting several subtypes of the smooth muscle myosin and decreasing the expression of α-smooth muscle actin and caveolin-1 proteins in CCSMC.[31,32] Studies have demonstrated that elevated levels of ROS and fibrogenic factors under high-glucose conditions can induce structural alterations, including smooth muscle atrophy and fibrosis, which ultimately impair smooth muscle diastolic function.[33] Also, oxidative stress can lead to an increase in CCSMC apoptosis.[34] In the CC of DMED rats, it was found to increase the apoptosis of CCSMC and extracellular matrix fibrosis,[35] resulting in the loss of normal contractile and diastolic functions of the CC.

Penile erectile function is complexly regulated by the hormones of the organism's endocrine glands and is significantly related to various hormonal pathways such as pituitary-testicular axes and thyroid function.[36,37] It is well known that androgens not only induce penile erection but also play a regulatory role in the process of CC blood perfusion and reflux to maintain the erectile state.[38] And adequate testosterone levels can regulate the expression and activity of PDE5 as well as endothelial function.[39,40] The reduction in serum testosterone levels has been identified as an independent determinant of penile vascular endothelial dysfunction. An animal experiment showed that DM condition affects the physiological functions of the hypothalamic-pituitary-gonadal axis in rats,[41] leading to a decrease in gonadotropin release and testosterone synthesis.[41] Moreover, DM can also increase apoptosis in germ cells by influencing B-cell lymphoma-2 and cysteine-dependent aspartate-directed proteases.[42]

The autonomic nervous system regulates CC blood flow, whereas activation of the peripheral nervous system induces contractions in the bulbo-cavernous and ischiocavernosus muscles.[4] In DM, the adrenergic and cholinergic autonomic nerves innervating the penile vasculature are impaired. This dysfunction leads to an imbalance in arteriovenous contraction during penile erection, reduced expression of nNOS,[43] and consequently diminished NO secretion. Also, diabetic peripheral neuropathy can cause sensory impulses from the penis to be transmitted to the erection reflex center, thereby reducing the contraction force of the cavernous muscles.[44] The mechanisms by which DM neuropathy affects erectile function are complex, involving multiple factors such as increased oxidative stress and decreased NOS activity.[45]

Limitations of DMED Treatments

DMED is one of the hard-to-treat ED subgroups. Despite significant progress in this field, it still faces many challenges. Based on the literature, the main treatment strategies for DMED include lifestyle interventions, psychosexual therapy, pharmacotherapy or non-pharmacological therapy, and penile prosthesis therapy.[4,8,46] Among them, lifestyle intervention is often supplemented with psychotherapy according to the patient's psychological condition, which can also alleviate underlying psychological problems. At present, the PDE5 inhibitor has been accepted as the standard of treatment for DMED. For patients exhibiting suboptimal therapeutic response to PDE5 inhibitors, contraindications for their use, or intolerance to adverse effects, alternative therapeutic approaches should be considered. Cayetano-Alcaraz et al reviewed antioxidant supplementation, intracavernosal injection therapy, intraurethral/topical alprostadil, vacuum erection devices, penile prosthesis, stem-cell therapy, low-intensity extracorporeal shock wave in the treatment of those DMED patients who have unsatisfied efficacy in PDE5 inhibitor therapy,[47] and each of the mentioned therapeutics have its limitations and adverse effects. These limitations have been briefly listed in Figure 1.

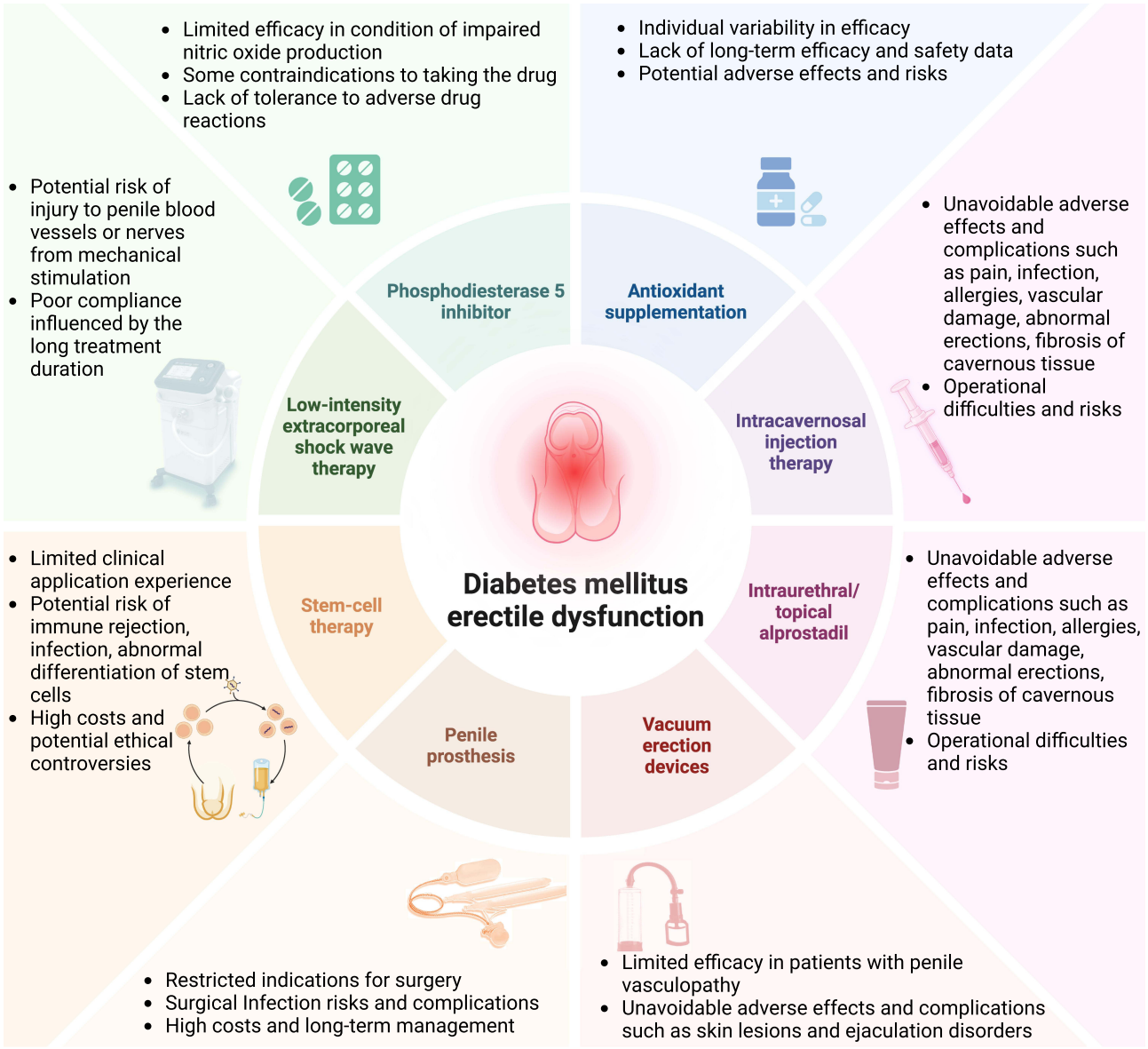

Figure 1 Available treatments for DMED and their limitations (Created in BioRender. Wang, (H) (2025) https://BioRender.com/i62y216).

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Medicinal Plants in DMED

Application of Medicinal Plants in DMED

Previous studies have reviewed the role of medicinal plants in ED. Since ED can be categorized into various subtypes, there are few reviews of medicinal plants in DMED. We summarize current experiments on medicinal plants and some of their active ingredients in DMED in Table 1 and Table 2 to elucidate their targets of action and related mechanisms.

Butea superba enhanced penile erection in DM rats by increasing the intracavernous pressure,[58] while Dracaena arborea is thought to possess aphrodisiac properties capable of alleviating DMED rats.[59] Ferula elaeochytris root extract administration to DMED rats has been shown to reduce glucose levels and recover neurogenic and endothelial dysfunction, but the authors did not confirm the possible mechanisms of action.[60] To explore the mechanisms of

Table 1 Experiments About Medicinal Plants in DMED

Plant	Extraction method	Subject of intervention	Result	Related Mechanisms	Ref.
Mucuna pruriens (Linn).	Ethanolic extracts	Wistar rats	[a]ROS, lipid peroxidation [b]nonenzymic antioxidants, catalase, superoxide dismutase, glutathioneper, glutathione reductase, glutathione-S-transferase, nitrite and nitrate oxidase	Oxidative stress	[48]
Gynochthodes officinalis (F.C.How) Razafim and B. Bremer	fermentation	SD rats	[a]malondialdehyde, caspase-3, caspase-9, B-cell lymphoma-2-associated X [b]max ICP/MAP raio, superoxide dismutase, cGMP, PI3K, p-Akt/Akt, p-endothelial NOS, endothelial NOS, neuronal NOS, α-smooth muscle actin	PI3K/Akt/ endothelial NOS pathway oxidative stress apoptosis	[49]
Red ginseng	Dissolution in saline	SD rats	[a]malondialdehyde [b]ICP, glutathione	Oxidative stress	[50]
Pentaclethra macrophylla leaves	fine powder	Wistar rats	[a]arginase activity, PDE5 [b]NO	NO/cGMP pathway	[51]
Pomegranate	Pomegranate juice	SD rats	[a]malondialdehyde [b]ICP/MAP ratio, smooth muscle cell/collagen ratio	Oxidative stress	[52]
Radix S. miltiorrhiza	aqueous extracts	SD rats	[a]ROS, malondialdehyde, glucose-regulated protein 78, C/EBP homologous protein, cleaved caspase-3, apoptotic cells. [b]superoxide dismutase, smooth muscle cell density	Oxidative stress apoptosis	[53]
Tribulus terrestris	Ethanolic extracts	Wistar rats	[a]luteinizing hormone [b]follicle stimulating hormone, testosterone	Hormone levels	[54]
Eucommia ulmoides Oliv. Leaf	Water extracts	SD rats	[a]malondialdehyde [b]ICP/MAP ratio, NO, cGMP, Serum superoxide dismutase, glutathione peroxidase, gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, and testosterone	oxidative stress hormone levels NO/cGMP pathway	[55]
Almond fruits	Fine powder	Wistar rats	[a]ROS, acetylcholinesterase [b]nuclear erythroid-2-related factor 2, smooth muscle/collagen ratio, total thiol and non-protein thiol	Oxidative stress	[56]
Cordycep militaris	Fruiting bodies	SD rats	[a]malondialdehyde [b]max ICP/MAP raio, testosterone, NOS, superoxide dismutase	Oxidative stress hormone levels NO/cGMP pathway	[57]
Butea superba (Roxb).	Ethanolic extracts	SD rats	[b]ICP	/	[58]
Dracaena arborea (Dracaenaceae)	Ethanolic extracts	Wistar rats	[b]sexual behavior	/	[59]
Ferula elaeochytris root	Extracts	Wistar rats	[a]glucose levels [b]ICP/MAP raio, spermatogenesis in testicles, testicle weights, nitrergic and neurogenic responses	/	[60]

Notes: [a]represents the inhibition effect, [b]represents the promotion effect.

Abbreviations: SD, Sprague Dawley; ROS, reactive oxygen species; cGMP, cyclic guanosine monophosphate; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; NOS, nitric oxide synthase; NO, nitric oxide; PDE5, phosphodiesterase-5; ICP, intracavernosal pressure; MAP, mean arterial blood pressure.

Table 2 Experiments About Ingredients of Medicinal Plants in DMED

Source	INGREDIENTS	Subject of intervention	Result	Related Mechanisms	Ref.
Epimedium	Icariside II	Rats and corpus cavernosum smooth muscle cells	[a]receptor of advanced glycation endproducts, malondialdehyde, reactive oxygen species, light chain 3-II/I, Beclin-1, advanced glycation end products, TFG-β1 /Smad 2 signaling pathway, apoptotic index [b]max ICP/MAP ratio, endothelial NOS, neuronal NOS, superoxide dismutase, α-smooth muscle actin, p-Akt, p-mTOR, NOS activity, cGMP, Ang II, testosterone, vascular endothelial growth factor	Oxidative stress NO/cGMP pathway hormone levels autophagy TFG-β1/Smad 2/connective tissue growth factor pathway apoptosis	[61–65]
Epimedium	Icariin	SD rats	[a]ROS, superoxidase dismutase, lactate dehydrogenase, B-cell lymphoma-2-associated X, cleaved caspase-3, TFG-β1/Smad2 signaling pathway [b]ICP/MAP ratio, endothelial markers, α-smooth muscle actin, B-cell lymphoma-2, smooth muscle/collagen ratio and endothelial cell content in the corpora cavernosa, α-smooth muscle actin, neuronal NOS, endothelial NOS	PI3K/Akt-signal transducer and activator of transcription 3 pathway apoptosis oxidative stress TFG-β1/Smad2 pathway	[66,67]
Zingiberaceae	Curcumin	White albino rats (Cux1: HEL1)	[a]NF-κB, p38, and inducible NOS [b]ICP/MAP ratio, cGMP, heme oxygenase-1, endothelial NOS, neuronal NOS, nuclear transcription factor-erythroid 2	NO/cGMP pathway inflammation	[68,69]
Zingiberaceae	Curcumin-Loaded Nanoparticles	Zucker diabetic fatty rats	[a]NF-κB activating protein [b]ICP/systemic blood pressure ratio, heme oxygenase-1	Inflammation	[70]
P. ginseng	Ginsenoside Rg3	SD rats	[a]cleaved caspase-3, apoptosis, malondialdehyde [b]ICP/MAP ratio, smooth muscle actin, platelet endothelial cell adhesion molecule-1, the number of positively stained nerve fibers, B-cell lymphoma-2, B-cell lymphoma-extra large, superoxide dismutase	Apoptosis oxidative stress	[71]
P. notoginseng	Panax notoginseng Saponins	SD rats	[a]malondialdehyde, apoptosis index, advanced glycation end products [b]ICP/MAP ratio, superoxide dismutase, glutathione, Akt, endothelial NOS, NO, cGMP	NO/cGMP pathway oxidative stress apoptosis	[72,73]
Coptis chinensis	Berberine	SD rats and corpus cavernosum smooth muscle cells	[a]malondialdehyde, ROS, Ras homolog family member A, Rho-associated kinase 1, Rho-associated kinase 2, janus kinase 2, sphingosine kinase 1, sphingosine 1-phosphate receptor 2, sphingosine-1-phosphate, p38 MAPK, extracellular regulated protein kinase 1/2, JNK 1/2/3, apoptotic rate, B-cell lymphoma-2 associated agonist of cell death, B-cell lymphoma-2 associated X/B-cell lymphoma-2 ratio, cleaved caspase-9, caspase-3, cleaved caspase-3, TGF-β1, collagen I, and collagen IV [b]max ICP/MAP ratio, superoxide dismutase, endothelial NOS, NO, cGMP	Ras homolog family member A/Rho-associated kinase pathway NO/cGMP pathway oxidative stress apoptosis sphingosine kinase 1/sphingosine-1-phosphate/sphingosine 1-phosphate receptor 2 and MAPK pathways	[74,75]

(*Continued*)

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Table 2 (Continued).

Source	INGREDIENTS	Subject of intervention	Result	Related Mechanisms	Ref.
Scutellaria baicalensis	Baicalein (BE, 5,6,7-trihydroxyflavone)	SD rats	[a]arginase II, p38 MAPK, reactive oxygen species, malondialdehyde, NADPH oxidase 1, TFG-β1, connective tissue growth factor, collagen I, collagen IV [b]max ICP/MAP ratio, endothelial NOS, NO, cGMP, L-arginine, superoxide dismutase, α-smooth muscle actin oxidase	NO/cGMP pathway p38 MAPK/arginase II/L-arginine pathway oxidative stress	[76]
Mulberry fruit	cyanidin-3-O-β-D-glucopyranoside	SD rats	[a]8-hydroxy-2-deoxyguanosine, corporal apoptosis, [b]ICP/MAP ratio, superoxide dismutase, endothelial NOS, neuronal NOS	Apoptosis oxidative stress NO/cGMP pathway	[77]
Ganoderma	Ganoderma lucidum polysaccharide	SD rats	[a]oxidative stress, apoptosis, TGF-β1, p-extracellular regulated protein kinase 1/2, p-JNK, arginase II [b]ICP/MAP ratio, testosterone, cGMP, NOS	NO/cGMP pathway extracellular regulated protein kinase/JNK pathway apoptosis oxidative stress	[78]
Tribulus terrestris	Gross saponin of Tribulus terrestris	SD rats	[a]ROS, tissue inhibitors of metalloprotease-1, cleaved caspase-3, cleaved caspase-9, apoptotic index [b]ICP/MAP ratio, NO, cGMP, endothelial NOS	Antiapoptosis oxidative stress NO/cGMP pathway	[79]
Moutan Cortex root	Paeonol	SD rats and corpus cavernosum smooth muscle cells	[a]high mobility group box 1/receptor for advanced glycation end-product/NF-κB pathway, NLR family pyrin domain-containing 3 inflammasome, TGF-β1, interleukin—1β, Smad 2/3, connective tissue growth factor, apoptosis index [b]max ICP/MAP ratio, endothelial NOS, NO, cGMP, α-smooth muscle actin	High mobility group box 1/receptor for advanced glycation end-product/NF-κB pathway apoptosis pyroptosis	[80]
Grapes and numerous plant species	Resveratrol	rats	[a]phosphodiesterase-5, superoxide, ROS [b]ICP/MAP ratio, neuronal NOS, endothelial NOS, cGMP	NO/cGMP pathway oxidative stress	[81,82]
Eugenia caryophyllata	Eugenol	SD rats	[b]ICP/MAP ratio	K^+channels	[83]
Vegetables and fruits	Quercetin	SD rats	[a]thiobarbituric acid-reacting substance [b]ICP, endothelial NOS, superoxide dismutase, nitrate/nitrite	Oxidative stress	[84]
Numerous fruits and vegetables	Ellagic acid	Wistar rats, isolated rat corpus cavernosum smooth muscles	[a]advanced glycation end products in isolated rat corpus cavernosum [b]sexual function	/	[85]

Notes: [a]Represents the inhibition effect, [b]represents the promotion effect; p- represents phosphorylation.

Abbreviations: SD, Sprague Dawley; TGF-β1, transforming growth factor-β1; NOS, nitric oxide synthase; NO, nitric oxide; cGMP, cyclic guanosine monophosphate; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; NF-κB, nuclear factor kappa-B; MAPK, mitogen-activated protein kinase; RhoA, Ras homolog family member A; Smad, small mothers against decapentaplegic; JNK, c-Jun N-terminal kinase; ICP, intracavernosal pressure; MAP, mean arterial blood pressure; ROS, reactive oxygen species.

medicinal plants in DMED, Suresh et al analyzed the mechanisms of mucuna pruriens on DM-induced erectile tissue damage, and the results indicated that ROS, superoxide dismutase, catalase, etc. were significantly improved in the penile tissue of DM rats after mucuna pruriens treatment.[48] Other studies showed red ginseng, pomegranate and almond fruits have the potential for antioxidant effects based on restoration of intracavernosal pressure reduced by DM.[50,52,56]

Salvia miltiorrhiza Bunge has antioxidative, anti-inflammatory, and antifibrotic properties and can regulate programmed cell death.[86] Danshen injection is a Chinese medicine injection whose main ingredient is Salvia miltiorrhiza Bunge. Studies showed that it could improve erectile function in DMED rats via increased erection times.[53] The therapeutic mechanisms are mediated through attenuation of penile tissue apoptosis via caspase-3 activation inhibition coupled with oxidative stress reduction. These effects occur concomitantly with downregulation of the endoplasmic reticulum stress biomarkers such as 78-kDa glucose-regulated protein and C/EBP homologous protein.[53] In addition, Gynochthodes officinalis (F.C.How) Razafim and B.Bremer is a lianoid shrub found in China, and its root is a common herb in traditional Chinese medicine (TCM) and also has effects on improving reproductive and sexual function.[87] Vitro experiments confirmed that it protected CCSMC and Schwann cells from apoptosis.[49] Their results also showed the protein expressions of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/eNOS pathway were upregulated in DMED rats after fermented or unfermented Gynochthodes officinalis (F.C.How) Razafim and B.Bremer treatment, while the level of oxidative stress was significantly reduced.[49]

Medicinal plants also have a role in regulating the NO/cGMP pathway. Nwagwe et al revealed that Pentaclethra macrophylla leaves supplemented diets caused a significant reduction in blood glucose levels and augmented erectile function by inhibiting arginase and PDE5 activities as well as enhancing NO level.[51] Fu et al investigated the effects of Eucommia ulmoides Oliv. Leaf extract on restoring erectile function in streptozotocin-induced DM rats model, and the results showed it promoted the NO/cGMP pathway, serum superoxide dismutase and glutathione peroxidase levels and reduced serum malondialdehyde levels.[55] Furthermore, Eucommia ulmoides Oliv. Leaf extract is likely to benefit the hypothalamic-pituitary-gonadal axis, sexual hormone and hormone receptor expression.[55] Similarly, extracts of tribulus terrestris and Cordycep militaris can also reverse the reduction of testosterone in DMED rats.[54,57]

Active Ingredients of Some Medicinal Plants for DMED

Studies demonstrate that the active ingredients of medicinal plants ameliorate DMED through CC relaxation via K+ channels,[83] and potentiation of the NO/cGMP pathway via upregulated NOS, cGMP, and PDE5 inhibition in the CC of DMED rats. And these active ingredients concomitantly reverse DM-induced testosterone reduction, mitigate oxidative stress, and suppress apoptosis—critical processes for attenuating CC fibrosis and restoring endothelial function.[76–82,84] The active components of medicinal plants combined with PDE5 inhibitors can improve erectile function in DMED rats and potentially exert a synergistic effect.[85] It is worth mentioning that icariside, curcumin, saponin and berberine are relatively common in basic research in the field of DMED.

Epimedium is the whole grass of the Epimedium brevicornum, a plant of the Berberidaceae Epimedium. The main active ingredients of Epimedium are flavonoids, mainly including icariin, icariside I, icariside II, etc. Icariin preserved penile hemodynamics, smooth muscle and endothelial integrity of DM rats by improving the smooth muscle/collagen ratio, endothelial cell content, and the expression of eNOS and nNOS in the CC.[67] Wang et al explored the mechanisms through which icariin enhances the efficacy of adipose-derived mesenchymal stem cells in the treatment of DMED and found icariin significantly inhibited the up-regulation of apoptosis-related proteins under oxidative conditions while promoting the expression of the anti-apoptotic factor.[66] These positive effects were accompanied by the activation of the signaling molecules PI3K/Akt and signal transducer and activator of transcription 3.[66] Icariin II can increase the intracellular cGMP, nNOS expression and NOS activity in rat CC tissues in vitro.[64] Also, several studies showed that icariin II could increase smooth muscle cell/collagen fibril proportions and α-smooth muscle actin to prevent atrophy of CC smooth muscle and CC fibrosis.[61,63,65] The specific mechanisms of these effects may be related to regulating testosterone and the programmed cell death, anti-oxidative properties, and the PI3K-Akt-mammalian target of rapamycin pathway.[61–63,65] Nonetheless, co-administration of icariin II and insulin exhibits enhanced therapeutic efficacy in improving erections compared with icariin II alone in DMED rats.[65]

Curcumin is a fat-soluble polyphenolic compound extracted from the rhizome of turmeric, which is the main component of turmeric to exert pharmacological effects. Previous studies have shown that curcumin has pharmacological effects such

as anti-oxidative stress, anti-inflammatory, anti-fibrotic, and anti-tumor,[88] and has been used in male sexual dysfunction.[89] Curcumin is involved in erectile signaling through increased eNOS, nNOS and cGMP expression in DMED rats.[68] NOS synthesis and release are involved in the NO/cGMP pathway, which directly affects penile erection. It is worth mentioning that heme oxygenase/carbonic oxide systems may complement or substitute the NOS/NO/cGMP system in cavernous tissue.[90] Heme oxygenase-1-derived carbonic oxide has a positive effect on cGMP levels in vascular endothelial cells.[90] A significant reduction of heme oxygenase-1 has been found in the cavernous tissue of DMED rats, and the heme oxygenase-1 reduction can be reversed by curcumin.[69] Also, studies showed that the expression of nuclear factor kappa-B and p38 significantly increased in DMED rats, and the administration of curcumin can lead to a significant reduction in their gene expression.[68,69] This further suggests that curcumin treating DMED may be related to its modulation of inflammation-related signaling pathways. In addition to internal administration, the topical application of curcumin-loaded nanoparticles also demonstrated similar anti-inflammatory effects on the corporal tissue of DMED rats.[70]

Ginsenoside Rg3, a trace tetracyclic triterpenoid saponin present in ginseng, has pharmacological effects that selectively inhibit tumor cell infiltration and metastasis, and is mainly used in oncological diseases.[91] In DMED, Liu et al explored the mechanism of ginsenoside Rg3 in terms of antiapoptosis and anti-oxidative properties, and they found that daily gavage of 100 mg/kg ginsenoside Rg3 in DMED rats can repair the damaged cavernous smooth muscle and vascular endothelium with the inhibition of cleaved caspase-3, malondialdehyde, and promotion of b-cell lymphoma-2, b-cell lymphoma-extra-large, and superoxide dismutase.[71] Similar to ginseng, Panax notoginseng also belongs to the Araliaceae family and ginseng genus, and is rich in saponins.[92] The Panax notoginseng saponins can down-regulate the expression of inflammatory factors, promote the growth of vascular endothelial cells, and regulate the function of endothelial cells.[93] Panax notoginseng saponins improved the DMED via the NO/cGMP pathway and restored the function of endothelium in CC of rats while at the same time, limiting the accumulation of AGEs and inhibiting cell apoptosis.[72] Panax notoginseng saponins can also suppress oxidative stress in CC of DMED rats, such as increasing the superoxide dismutase and decreasing the malondialdehyde.[73] While Akt is involved in cell survival and oxidative stress inhibits Akt activity, the suppression of oxidative stress by Panax notoginseng saponins may restore Akt-mediated protection of CCSMC and vascular endothelial cells in CC of DMED rats.[73]

Berberine is an isoquinoline alkaloid extracted from Rhizoma Coptidis, which is the most abundant and valuable monomer among the active ingredients of Rhizoma Coptidis. Berberine can improve DM and its complications. Previous experiments confirmed that berberine could improve the erectile function of DM rats by inhibiting Janus kinase 2 and reducing oxidative stress.[74] In addition, berberine has many other effects such as regulating the sphingosine 1-phosphate receptor 2/mitogen-activated protein kinase signalling pathway to ameliorate DMED rats. In Liu et al study, DM induced the high expression of sphingosine kinase 1, sphingosine 1-phosphate receptor 2, and sphingosine-1-phosphate in the penile tissue of rats, and these indicators could be partially suppressed by berberine.[75] Furthermore, supplementation with berberine inhibited the expression of transforming growth factor-β1, collagen I/IV, and apoptosis indicators caused by DM in the penile tissue of rats.[75]

Advantages of Medicinal Plants for DMED Treatments

Previous studies on DMED mechanisms involve multiple pathways that may influence CC relaxation and contraction, and the NO/cGMP pathway remains a crucial target for DMED. PDE5 inhibitor is accepted as the first-line treatment for ED.[1,94] Recently, many studies have explored the potential of combination therapies for the treatment of DMED.[95,96] The main targets of action of the medicinal plants mentioned in Table 1 and Table 2 are also focused on the regulation of the NO/cGMP pathway, and it is noteworthy that they also promote the production of NO, eNOS, and nNOS. Furthermore, the antioxidative properties and apoptosis-regulating capacity inherent to medicinal plants synergistically enhance penile endothelial and smooth muscle function through multi-mechanistic pathways. Despite limited clinical data on the use of medicinal plants in combination with PDE5 inhibitors for the treatment of DMED, animal studies showed that dosing with ellagic acid, sildenafil, and the combination of both increased the sexual function of DM rats. Sildenafil was more effective than ellagic acid, and the combination of both was the most effective in managing DM-induced sexual dysfunction.[85] Similarly, the combination of novel water-soluble curcumin derivative with sildenafil had a more obvious effect on improving NOS activity compared to either soluble curcumin derivative or sildenafil alone.[69]

TCM therapy for DMED is widely used In some East Asian countries, and it is characterized by the prescription of several medicinal plants through TCM perspective to achieve individualized treatment.[97] In terms of TCM theory, the causes of ED are related to kidney yang deficiency, qi deficiency, and blood stasis, etc. TCM believes that many medicinal plants such as Eucommia ulmoides Oliv. Leaf, and Epimedium can tonify kidney yang, red ginseng can tonify qi, and Radix S. miltiorrhiza can remove blood stasis. However, there is still a lack of research on whether the prescription of multiple medicinal plants is superior to a single medicinal plant treatment in improving erectile function in patients with DMED. The effects of a nutritional supplement composed of Panax ginseng, Moringa oleifera and rutin have been evaluated as single or combined agents in DMED rats, and the results showed that the mixture of these three medicinal plants was more effective in improving sexual behaviour compared with any single one of these three medicinal plants.[98] It is undeniable that prescriptions of multiple medicinal plants improve erectile function in patients with DMED.[97] From TCM perspectives, these prescriptions have specific effects, such as tonifying the kidney, regulating the liver, and promoting better blood flow to various organs. Current studies of the compound composition of TCM and animal model also suggest that these prescriptions of medicinal plants contain multiple pharmacodynamic components, such as icariside and curcumin (Table 2), and these prescriptions can serve as multi-targeted treatment of DMED through different pathways.[99–101] Therefore, combining the application of medicinal plants with the theoretical perspectives of TCM to form prescriptions seems to be a "holistic" therapeutic approach.

Challenges in the Use of Medicinal Plants in DMED

We briefly review that DM-induced ED is refractory, mainly due to the complexity of the involved mechanisms and the limitations of available treatments. We also discuss the potential of medicinal plants and their active ingredients in DMED. Although current animal experiments have established a certain foundation, They have at least confirmed some targets and pathways of action for medicinal plants and their active ingredients in treating DMED. However, we admit that there are still many challenges in the research on medicinal plants in the field of DMED (Figure 2).

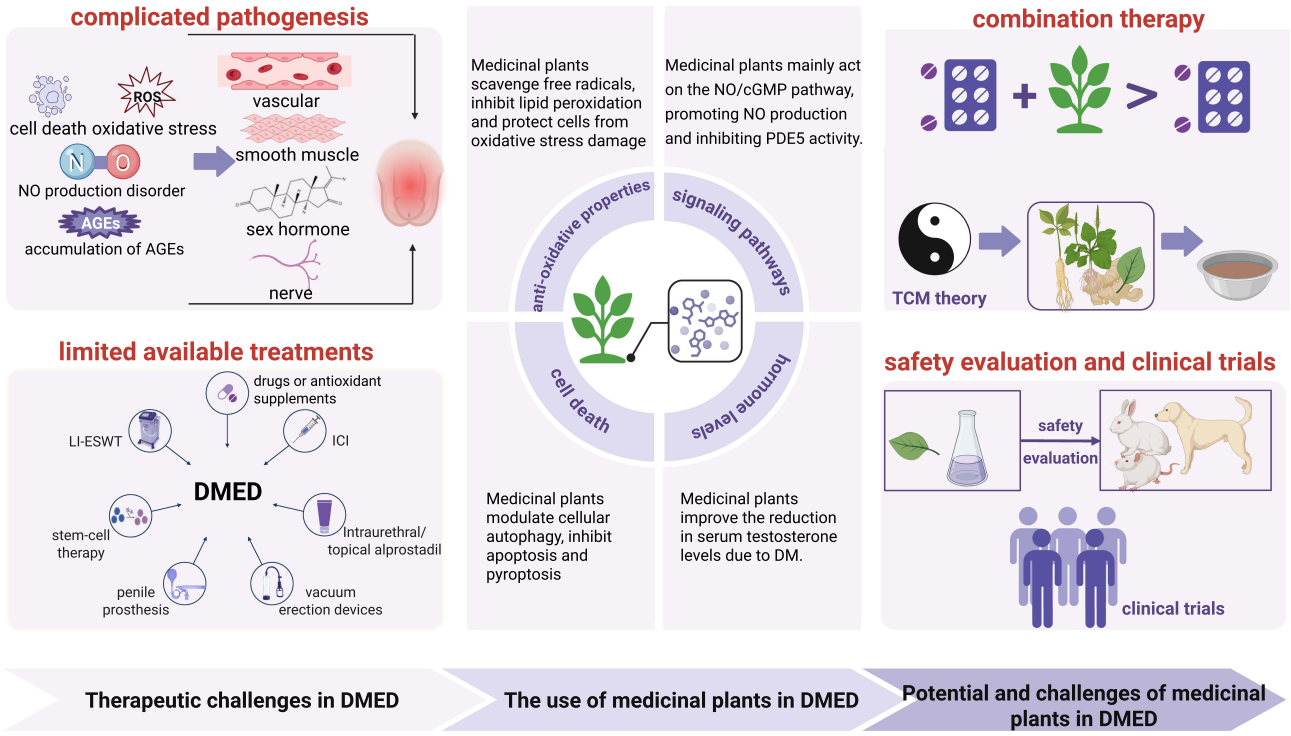

Figure 2 Therapeutic challenges in DMED and potential of medicinal plants (Created in BioRender. Wang, (H) (2025) https://BioRender.com/b36d664).
Abbreviations: NO, nitric oxide; AGEs, advanced glycation end products; ROS, reactive oxygen species; DMED, diabetes mellitus erectile dysfunction; cGMP, cyclic guanosine monophosphate; TCM, traditional Chinese medicine; PDE5, phosphodiesterase-5; ICI, intracavernous injection; LI-ESWT, low-intensity extracorporeal shock wave therapy.

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There are many clinical studies on the application of medicinal plants in the treatment of ED,[102,103] but few studies in DMED. On the one hand, DMED is a type of refractory ED, often accompanied by vascular and neural injuries, etc. It may be difficult to ensure the efficacy of using medicinal plants alone. In a randomized controlled trial, the authors investigated the effects of a topical saffron gel on ED in DM men, the intervention group was treated with topical saffron, and the control group received a similar treatment with a placebo.[104] After 1-month treatment, the prepared saffron gel was significantly more effective than placebo on erectile function score.[104] Nevertheless, due to the difference between DMED and nonorganic ED, the authors did not describe the underlying treatment management involved in the participants during the study, including glucose-lowering regimens, daily life coaching, and so on.[104] Also, there might be some limitations, such as ethical controversies, when applying a placebo only to the control group. Therefore, many researchers often use the guideline-recommended treatment option to treat DMED patients in the control group, and they regard the medicinal plant as a complementary and alternative therapy and used it in combination with the recommended treatment option in the guideline for the treatment group.[105] This is also in line with practical clinical applications.

In Table 1 and Table 2, the basic studies evaluating the relevance of medicinal plants to DMED treatment did not report any adverse effects or toxicity. However, this may be because most of them were drug discovery or mechanism studies rather than toxicity studies. Thus, the focus of these studies has been on elucidating active plant constituents or mechanisms of action rather than on safety assessment. Medicinal plants and their active ingredients are generally considered safe because they are "natural". However, various factors such as the inherent toxicity of plants and natural products, contamination, and exact formulations may affect their safety profile. This also seems to imply that achieving substantial clinical translation and realizing the benefits of medicinal plants still have a long way to go.

Future Recommendation in the Use of Medicinal Plants on DMED

The pathogenesis of DMED involves vascular, neurological, endocrine, and other factors. Based on our review, medicinal plants exert their effects through a wide range of mechanisms, including vascular endothelial protection, sex hormone regulation, and antioxidant activity. Therefore, it is necessary to further isolate the active components (such as flavonoids and saponins) in medicinal plants and reveal their effects on the targets related to DMED through molecular biology techniques in the future. And clarifying the long-term safety of plant active ingredients, drug metabolism pathways, and interaction risks of co-administration with some hypoglycemic agents through animal model interventions will also be beneficial to the medication safety. In addition, with the wide application of multi-omics technology, systematic analysis of the effects of medicinal plants on the metabolic network of DMED patients is also helpful to provide a basis for precise medication.

Due to the complexity of the pathogenesis of DMED, it is difficult for medicinal plants to have the same rapid clinical efficacy as PDE5 inhibitors. However, we have to admit that phytotherapy considers multiple aspects including neurological, vascular, and endocrine in the treatment of DMED.[106] This suggests that medicinal plants may serve not only as complementary and alternative therapies but could also be used in combination with PDE5 inhibitors for managing DMED, as well as improving other symptoms induced by DM.[107,108] Therefore, further clinical trials are needed to validate the efficacy and safety of medicinal plants for DMED and to explore combination therapies that may offer comprehensive therapeutic solutions.

Topical medications are beneficial in alleviating the adverse effects associated with oral medications and may also increase adherence to treatment.[109] Studies have demonstrated the potential of topical application of PDE5 inhibitors in the treatment of ED,[110] and localized inflammatory responses in the penile tissue of DMED rats have also been alleviated by curcumin-loaded nanoparticles.[70] Despite the lack of relevant studies, the encapsulation of active ingredients from medicinal plants using nanotechnology, along with the enhancement of their bioavailability and targeted delivery to the cavernous body of the penis or neurovascular tissue, remains necessary to reduce systemic adverse effects.

Conclusion

We review the complicated pathogenesis and current treatment limitations in DMED, explores the therapeutic applications, potential, and challenges of medicinal plants and their active ingredients, and proposes future research recommendations for this field. Although our review demonstrated the advantages of medicinal plants and their active ingredients in regulating NO/cGMP pathway, cell death, oxidative stress, and sex hormone levels, relevant studies are still lacking, especially high-level scientific evidence and a better understanding of the dose, toxicity, and metabolic mechanisms. At the same time, clinical trials

of using the medicinal plant alone or in combination with other therapeutic options are still necessary to evaluate their efficacy and safety for DMED patients.

Data Sharing Statement

Data supporting this article is readily available upon request and in public domains.

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, manuscript drafting, revising or critical review. All authors consented to the final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. No Artificial Intelligence tools have been used in the drafting of this manuscript.

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Disclosure

The authors report there are no conflicts of interest in this work.

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