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Mechanisms and therapeutic opportunities in erectile dysfunction for advanced glycation end products (AGEs)

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Abstract

Diabetes mellitus (DM) is one of the world's most common diseases. Its impact on the male reproductive system is one of its key impacts. Up to 90% of diabetic men experience erectile dysfunction and decreased libido, which can result in infertility. Several researchers have investigated the negative impacts of reactive oxygen species and the subsequent development of oxidative stress that occurs due to DM. Non-enzymatic glycosylation products (AGEs) have been found in diabetic men's reproductive tracts. AGEs work by generating reactive oxygen species (ROS) or attaching to receptors on their own. The binding of AGE to the receptor (RAGE) has been demonstrated to play a role in physiological processes such as lung homeostasis, bone metabolism, neural systems, and the immune system. The human body has several defense against AGE accumulation, which are reduced in diabetic individuals. The situation can be improved by using some preventive measures, either by using oral drugs or natural therapeutic agents. Also, herbal medicine is gaining popularity in the market to treat various ailments. Because of the long cultural history of use and the present resurgent interest, using herbal treatments to manage male sexual dysfunction is beneficial.

Keywords: Diabetes, erectile dysfunction, male infertility, receptor for advanced glycation end products, reactive oxygen species

1. Introduction

Erectile dysfunction (ED), often known as impotence, is a condition in which a male experiences problems with his penile erection. Within 10 years of diagnosis, up to 50% of diabetic men suffer from ED (1). Fertility is also affected by a variety of factors like lifestyle factors, obesity, limited or absence of exercise, and lower urinary tract symptoms, and one of the most common of them is erectile dysfunction (2). In the United States, 30 million men suffer from ED, with a global prevalence incidence of 10-20% (3). The cavernosal and penile arterial smooth muscle walls play a significant role in the penile erectile tissue (4). Molecules involved in the erection pathway could be utilized as targets for the development of novel ED therapies (5). Diabetic-induced ED (DIED) is often resistant to PDE-5 inhibitor treatment (1).

During a long-term hyperglycaemic state in diabetes mellitus, glucose creates covalent adducts with plasma proteins, and this non-enzymatic process is known as glycation. Glycation of proteins and the production of advanced glycation end products (AGEs) are significant in the pathophysiology of diabetic complications such as retinopathy, nephropathy, neuropathy, and cardiomyopathy, as well as other diseases such as rheumatoid arthritis, osteoporosis, and aging (6). AGE levels in the testis, epididymis, and sperm are raised in hyperglycaemic conditions (7). Methylglyoxal (MG) is the precursor of AGEs and interferes with NO release (8, 9). Receptors of AGE (RAGE) present in the male reproductive system combine with reactive oxygen species, which initiate the damage of nuclear DNA (10).

AGEs show involvement in nitric oxide (NO) bioavailability, molecular pathways activated by receptors of AGEs, intercellular or intracellular deposition of insoluble complexes, and activity in cavernous tissue (11). In the penile tissues of diabetic patients, accumulation of AGEs (pentosidine) has been detected (12). Aminoguanidine prevents the formation of AGEs, in DIED (13). AGE production is known to trigger diabetes and is also connected to male infertility disruption (14). AGEs have been shown to limit testosterone production and secretion by Leydig cells by stimulating the generation of reactive oxygen species (ROS), which impacts male infertility (15). Intracavernosal vasoactive agent injections are the most effective treatment for DIED (16).

Natural products have been used since ancient times for the treatment of many diseases and illnesses. Glycation-induced ED can also be treated with natural products. By altering the NO/cGMP system, *Panax notoginseng* protects endothelial function in the penile corpus cavernosum (17). *Pausinystalia yohimbe* and *Epimedium grandiflorum* play a role as central sexual impulses as well as enhancing the release of NO from

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cavernosal endothelial cells (18). Therefore, in this review, we will talk about how glycation can affect erectile dysfunction and a therapeutic approach as well as natural products to minimize the effects. In this review, articles were identified in databases like PubMed, Google Scholar, Scopus, and Web of Science.

2. Erectile Dysfunction (ED)

Male infertility has a variety of causes, ranging from genetic mutations to lifestyle choices to medical illnesses (7). Some causes of male infertility are listed below in Fig. 1. The worldwide prevalence rate in hypogonadism is 9.6%, in retrograde 0.4-2%, in premature ejaculation 70%, and in ED 10-20% (19-21). Erectile dysfunction (ED) is the inability to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse (22). ED has a huge negative influence on a man's quality of life, causing him to lose self-esteem and intimacy and experience anxiety and despair, all of which increase sexual dysfunction. The most important etiological factors of organic ED are metabolic syndrome, cardiovascular disease, and diabetes mellitus (23). Any process or disease that affects penile arteries or nerves, smooth muscle tissue, hormone levels, the corporal endothelium, or tunica albuginea can be a reasonable cause of ED (24).

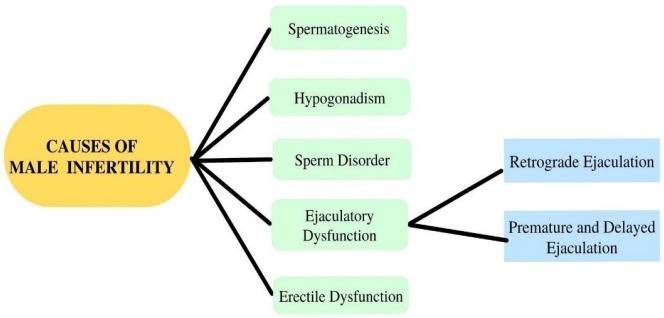

Fig. 1. Causes of male infertility

2.1. Risk factors of ED

Obesity, medications, heart disease, atherosclerotic disease, smoking, aging, diabetes, psychological stress, depression, vascular difficulties, and many more variables are linked to ED. Some of the psychogenic and organic factors responsible for ED are shown in Fig. 2. ED can also be caused by antihypertensive or antidepressant medications. In approximately 60% of men, diabetes mellitus is the cause of ED. 40% of diabetic males have hypogonadal symptoms (25). Controlling glycaemic and hypertension levels in diabetics is critical since these factors raise the risk of both microvascular and macrovascular problems, which might include ED (26). The timing of the onset should always be assessed. Gradual and progressive histories suggest an organic cause, whereas a sudden onset of complete ED in the absence of trauma or other obvious causes suggests a possible psychological cause (27).

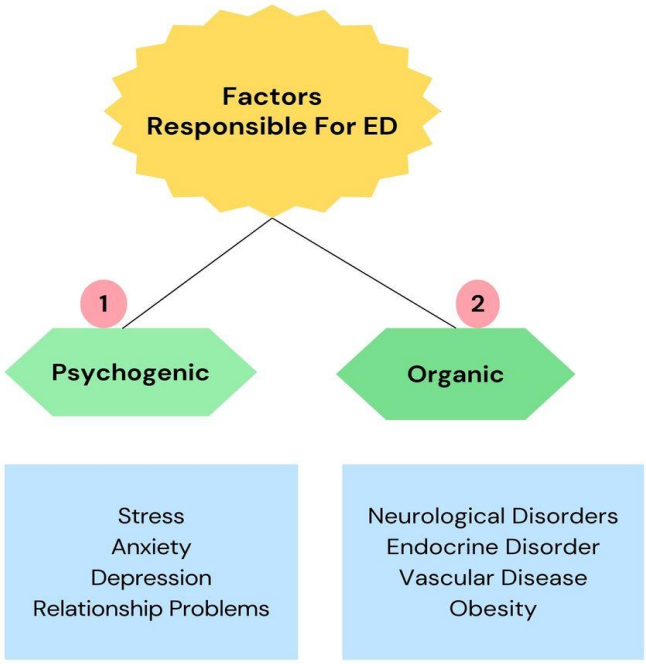

Fig. 2. Risk factors responsible for ED

2.2. Mechanism of Penile erection and ED

The integration of endocrine, vascular, psychologic, neurological, and local anatomical systems has been involved in the development of an erection (25). The non-adrenergic non-cholinergic nerve (NANC) neurotransmitter promotes vascular and cavernosal relaxation, increasing blood flow during erection (28). It is believed that the corpus cavernosum nerves and the corpus cavernosum sinusoidal endothelial cells of the penis release NO during erection; it is synthesized by neuronal NO synthase (nNOS) and endothelial NO synthase (eNOS), respectively. For normal sexual performance, nNOS initiates penile erection by producing NO, and eNOS participates in sustained erection by producing NO (29).

Guanosine triphosphate (GTP) is converted to cyclic guanosine monophosphate (cGMP) due to the diffusible nature of NO by the enzyme guanylate cyclase in penile SM (30). The elevation in the cGMP level results in the activation of protein kinase G, which causes phosphorylation of ion channels, which triggers arterial and trabecular SM relaxation and a decrease in intracellular calcium and potassium (31, 32). The penis erection increases due to arterial blood flow increasing into the lacunar spaces of the penis due to vasodilation, intracavernosal pressure rising by a veno-occlusive mechanism, and entrapment of the blood in the corpora cavernosa. These events collectively result in increased intracavernosal pressure, which leads to a full penile erection, as shown in Fig. 3. The sinusoidal small vessels of the penis are sensitive to endothelial structural and functional changes; even minor modifications lead to erectile dysfunction (33). It has been established that penile nerve terminals and vascular endothelium produce insufficient amounts of NO, which results in an impaired erection or complete impotence (34).

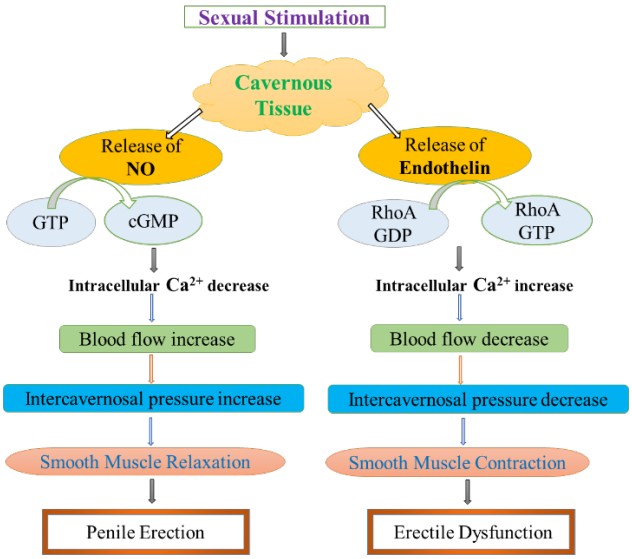

Fig. 3. Events involved in penile erection and its dysfunction

According to the researchers, ED in diabetics may be associated with an imbalance toward increased penile vasoconstriction as a result of endothelin (ET), its receptors, and ultrastructural alterations in the endothelium (35). Several studies have suggested that the endothelin (ET) transduction pathway and its receptor may be involved in diabetic ED. RhoA, a GTP-binding protein, and Rho-kinase, the pathway's effector, make up the pathway (36). The RhoA/Rho-kinase pathway has been found to be connected to ET-1-induced vasoconstriction. The route is activated, which inhibits eNOS and reduces NO generation. Rho-kinase has been found to be increased in diabetic rats and is present in rat, rabbit, and human cavernosal tissue (37). It is proposed that the RhoA/Rho-kinase pathway mediates ED through decreased production of NO in the penis. The RhoA/Rho-kinase pathway is thought to cause ED by reducing NO generation in the penis (38, 39).

3. Glycation

Glycation is a spontaneous non-enzymatically glycosylation reaction between the reactive carbonyl groups or free reducing sugars with nucleophilic free amino groups of proteins, DNA, and lipids that form an Amadori product (40). Glycation products are not stable, and they give rise to numerous and undefined degradation products known as AGEs (41).

3.1. Advanced glycation end products (AGEs)

AGEs are the modifications of proteins or lipids that become non-enzymatically glycated when modified with oxidized aldose sugars. Histopathological studies have shown the accumulation of AGEs in different tissues and dermal layers, including the renal cortex, coronary atheroma, and amyloid plaque in Alzheimer's disease, cardiac muscle, lung, and liver (42). AGEs can be classified into fluorescent AGEs, which include pentosidine and methylglyoxal-lysine dimer (MOLD), and non-fluorescent AGEs, which include carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), and pyrroline (43).

AGEs have developed different receptors, receptors of advanced glycation end products (RAGE), which mediate the intracellular signaling that disrupts cellular function through the recognition and binding of AGEs represented in Table 1 (44). The therapeutic options include AGE cross-link breaker, AGE inhibitor, RAGE antagonists, clinically approved drugs for antidiabetics, antihypertensive drugs, or statins, as well as dietary and phototherapeutic approaches (45).

Table 1. Classification of AGE receptors

Types of RAGE	AGER1	AGER2	AGER3	sRAGE
Another name	Oligosaccharide transferase-48	Phosphoprotein	Galectin-3	Soluble RAGE
Molecular weight	~48 kDa	~80-90 kDa	~26 kDa	~46-50 kDa
Location	endoplasmic reticulum and cytoplasmic membrane	Endothelial cells	Cytoplasm, nucleus, cell surface	Cell membrane, body fluid
Function	Endocytic uptake and degradation, protective role against the formation of reactive oxygen species, tissue injury	Cell activation	Cell activation and degrade AGEs moieties	Degradation and clearance

The production of AGEs results in the formation of NO as well as a reduction in free radical concentration, resulting in oxidative stress. NO is a vasodilator with an anti-proliferative impact on vascular smooth muscles. As a result of the accumulation of AGEs, hypertension, endothelial dysfunction, and vascular thickening with loss of elasticity occur (42). In patients without diabetes or infection, AGEs and RAGEs are connected with male infertility (46). According to the study, serum, and seminal plasma concentrations of soluble RAGE (sRAGE) show a variation between fertile and infertile men (46). The polyol pathway is activated due to hyperglycemia in the testis, and to investigate the pathway, sorbitol production in the testis and epididymis of mice is measured. This activation of the diacylglycerol pathway is measured by protein kinase C (PKC) in the testis and epididymis of mice. Maresch and his colleagues found that 12 to 24 weeks later, the testicular PKC value increased in diabetic mice compared to non-diabetic mice (14). Identification of CML and immunohistochemical analysis of AGE distribution revealed that the interstitium, Leydig cells, macrophages, and blood vessels are AGE-positive (47).

3.2. Effect of AGEs on ED

In the ED, there were 1.9–4 times more complaints in diabetic men than in non-diabetic men (48). ED has recently been considered the precursor to systemic vascular disease and the

earliest manifestation of atherosclerosis. High amounts of superoxide radicals are present in cavernosal tissue levels, and NO synthase is decreased in men with diabetic-induced erectile dysfunction (DIED) (49).

As shown in Fig. 4, HbA and glucose combine to form glucose and glycosylated hemoglobin, which are freely permeable red blood cells (RBCs). An intermediary, the Amadori product, produces HbA_{1c} formation, and Hb-AGE irreversible accumulation occurs. The formation of AGEs in DM is related to glycaemic control. Fluorescent pentose-mediated protein crosslinks pentosidine, an AGE product that is present in excess amounts in the corpus cavernosum of diabetic patients (50). It states that the preferential location for AGE accumulation is cavernous collagen fibers. AGEs also affect the different channels and receptors present in SM. For relaxation, intracellular calcium is essential, and it is released through potassium channels (11). The early onset of DIED happens due to early damage to potassium channels. The PDE isoform in the cavernosal SM-type 5 is inhibited by drugs, and it is responsible for the degradation of cGMP levels, which leads to an improvement in erection (51).

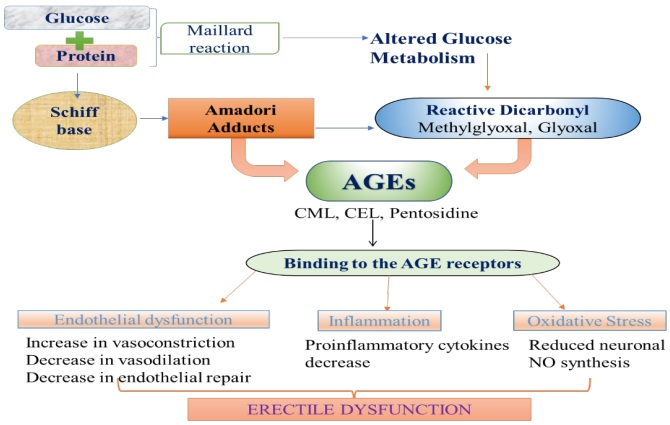

Fig. 4. Consequences of AGE formation on Erectile Dysfunction

AGEs are elevated in diabetic human penile tissues but not in serum and are localized to the collagen of the penile tunica and corpus cavernosum (52). AGEs form a covalent interaction with collagen, which leads to the thickening of the vascular wall and decreases its elasticity, which strongly leads to the dysfunction of cavernous tissue (53). AGEs affect diabetic ED patients by affecting oxygen free radicals, which elevate the oxidative cell damage and quench NO, decrease the cGMP, and impair SM relaxation (54). Some studies reveal that in diabetic animals, reductions in endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) cause SM contraction (54). Studies show that in the human penile cavernosal SM and endothelium, there is a presence of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) (52).

RAGE is attributed to an AGE-binding molecule expressed on cells of monocytes and macrophages, which mediate AGE cell uptake from blood and tissues (55). Macrophages and macrophage derivatives produce AGEs and accumulate these substances in their cytoplasm (56). In diabetic complications, AGEs, and their receptors interact to induce biological effects on the target tissues. Hyperglycemia increased oxidative stress and induced the polyol pathway, both of which are involved in the pathogenesis of diabetic neuropathy. Their effects were nerve tissue damage or vascular dysfunction (56).

AGEs production is one of the important causes of neuropathy (57). AGE receptor 1 (AGER1), or oligosaccharyltransferase-48 or OST-48, is a transmembrane protein present in the cytoplasmic membrane and endoplasmic reticulum (58). It exhibits significant AGE binding affinity, is involved in endocytosis, and contributes to the suppression of AGE-mediated mesangial cell inflammatory injury due to diabetes and aging (55, 59). AGER1 provides protection against AGE-induced ROS, which is generated via NADPH oxidase (60). Periodical oral exposure to methylglyoxal-derived AGEs loses protective effects; it induces the depletion of not only AGER1 but also SIRT1. The vascular protective effect of NAD^+-dependent deacetylase has been identified in the cavernous tissue of rodents and humans. When AGER3 is exposed to AGE, it gets translocated to the cell surface where it promotes endocytosis and degrades AGE moieties. Galectin-3 detection in SM of rat induced-AGE proliferation (11). Excessive deposition of AGEs attracts the monocytes and might bind to the vessel surface, migrate to the vessel wall, and release mediators that contribute to the development of vascular lesions (61). Various activities of the AGER system are modulated by diabetic factors, which include insulin, ROS, and AGEs. Diabetes, dyslipidaemia, and aging highly increased AGE formation, which increases RAGE expressions (55). Sperm nuclear DNA damage implies the presence of RAGE, particularly in diabetic men where the levels are elevated (10).

4. Therapeutic approach and strategies in AGE-induced ED

Several treatment options are available, most of which are associated with high-efficiency rates and safety profiles (62). There is evidence that suggests that for treating sexual dysfunction, pharmacological interventions or combined therapies are more effective than non-pharmacologic ones. Individual patients may consider the risks and benefits of treatment differently (63).

4.1. Oral treatment

PDE-5

Inhibitors of PDE-5 are the most effective oral drugs that help to inhibit the breakdown of intracellular cGMP and help to achieve and maintain an erection (64). Vardenafil (Levitra™), sildenafil (Viagra™), and tadalafil (Cialis™) are drugs in the family of PDE5 inhibitors and are mainly used in the treatment of ED (65). Vardenafil improves erectile function in men with mild to severe ED associated with diabetes mellitus. Oral vardenafil 10-40 mg increased penile rigidity (66). Vardenafil acts on endothelial cells and works as an anti-inflammatory by

reducing RAGE expression by elevating cGMP (67). Sildenafil is well-tolerated and effective -in patients with poor glycaemic control or chronic complications, and it is effective in men who are facing ED with Type II diabetes (68). In the general population, the efficacy of sildenafil is reported to be between 74–97%; it is only 50–56% among diabetic individuals (69). The onset of tadalafil is 2 hours, with a duration of efficacy of 36 hours and no interaction with food (70).

Aminoguanidine

Aminoguanidine (AG) inhibits the formation of highly reactive AGEs and inducible NO synthase (71). Several studies have shown that AG is used in the prevention of AGE formation and AGE-related complications (59). In diabetic conditions, it helps to reverse impairment in neuronal and endothelial NO-mediated penile SM relaxation (15). Usta and his colleagues (2004) found that one-month treatment with AG improved erectile function with no change in AGEs (72). In other words, in the penile vasculature, AG has protective effects through alternative pathways.

4.2. Intracavernosal injection

Intracavernosal injections (ICI) or combined drugs or vacuum constriction devices are included under second-line treatment. ICI is a vasoactive injection with high success rates. This class of drugs includes phentolamine, prostaglandin E1 (PGE-1), vasoactive intestinal peptide (VIP), and papaverine (51). PGE-1 is also known as alprostadil. In this treatment, medication is directly injected into the corpora of the penis at the lateral side (74). The erection lasts for a period of time depending upon the dose injected, and it begins after 5–15 minutes. Complications include penile pain, prolonged erection, priapism, hematoma formation, and penile fibrosis (75). Papaverine is a non-specific inhibitor that increases the level of cyclic adenosine monophosphate (cAMP) or cGMP to inhibit the Ca^{+2} channels and results in SM vasodilation and relaxation (76). Papaverine (30 mg) and phentolamine (1 mg) are collectively marketed as Androskat® and are commonly known as bimix (2 ml). Its efficiency rate is 94% and the incidence of side effects is 0.9-2.6%. Papaverine (30mg), phentolamine (1mg) and PGE1 (40g) combine to form a trimix. Trimix gives a longer-lasting erection than PGE-1 but may also increase the probability of priapism (77).

Table 2. Therapeutic treatment, functions, and side effects of ED

Therapeutic approach	Examples	Function	Side effect	General indications	References
Oral treatment	Phosphodiesterase-5 inhibitors -Vardenafil -Sildenafil -Tadalafil -Avanafil	The increase in cGMP level contributes to the establishment and maintenance of an erection.	Headache, flushing, dyspepsia, nasal congestion, back pain. After continued treatment, side effects may diminish.	First-line treatment	(51, 70, 73]
	Aminoguanidine	Reduced AGE formation in cavernosal tissue	Pancreatic and renal tumor		(11, 61]
Intracavernosal injection	Prostaglandin E-1 Papaverine Phentolamine	cAMP pathway activation Non-selective PDE-5 inhibitor Short-acting alpha-adrenergic receptor antagonist	Common effects include penile pain, bleeding, and bruises. Complicated effects: scar tissue, penile burning	First-line treatment	(51, 78]
Vacuum constriction devices	-	It helps in maintaining an erection.	Decrease in the quality of orgasm and ejaculatory discomfort, pain due to constriction ring	Second-line treatment	(76]
Penile implant	-	It helps to get an erection.	Risk of infection, penile pain, fever	Third-line treatment	(76, 85]

4.3. Vacuum constriction devices

Vacuum erection devices include a suction cylinder and pump, which boost corporal blood flow. A compression band is included at the base of the penis to maintain an erection by lowering corporal venous drainage. About 2–2.5 min is taken to obtain an erection (79). The vacuum constriction device is the safest, least expensive, and most prescribed treatment for men (80). A 100–225 mm Hg vacuum pressure is required to achieve an erection. Since 1982, the United States has approved Vacuum erection devices (81). Most patients quit early because the device may be ineffective, painful, or cumbersome. Moderate ED patients show a higher success rate (82).

4.4. Penile Implant

When pharmacological therapy fails or patients are not able to tolerate vacuum erection devices, then a penile prosthesis is introduced. It's a reliable way to restore an erection with good durability and patient satisfaction (83). There are two types of penile implants: non-inflatable or malleable and inflatable. Patients who can achieve near-normal erection or flaccidity are able to undergo inflatable implants. In secondary diabetes, malleable implants should be avoided due to the risk of erosion (54). After penile prosthesis implantation, the satisfaction rates of partners and patients are higher than those of those who are taking medications or using devices to restore erection (84).

5. Natural products as alternative approaches for the treatment of glycation-induced ED

Natural products have been used since ancient times for the treatment of many diseases and illnesses. About 35% of medicine originates from natural products (86, 87). Some of the plants listed below are used in the treatment of glycation-related ED.

5.1. Curcuma longa

Via upregulation of the heme oxygenase-1-gene and cyclic guanosine monophosphate, curcumin derivative erection is mediated (88). *C. longa* compounds like curcumin and diferuloylmethane show activity on the penile erection response. Oral intake of pure curcumin and water-soluble curcumin by albino male rats for a period result in increased activity of cavernous tissue and heme oxygenase enzyme-1 activity is involved in the penile erectile mechanism (89). A polyphenolic compound of *Curcuma longa,* curcumin may protect carbonyl stress-induced endothelial cells by trapping dicarbonyl compounds (90).

5.2. Epimedium grandiflorum

The genus *Epimedium* includes more than 50 plant species, many of which have been used to treat infertility for over 2000 years (93). Horny goat weed is an active ingredient of icariin, a flavanol glycoside obtained from the aerial part of epimedium (94). Glycoside and its derivatives have been used to increase NO synthesis in the penis, have a positive neurotropic effect on nitrergic nerves, decrease AGEs, and enhance SM proliferation (18). Icariin has enhanced erectile function in its bioactive form, icariside II (95). Icarisid II elevates the intracellular cGMP levels by enhancing nNOS expression and NOS activity in rat corpus cavernosum tissues (96). The upregulation in AGE concentration and downregulation of the NO-cGMP pathway in diabetic ED leads to a decrease in erectile function (95).

5.3. Ginkgo biloba

The release of endothelial NO improved ED which is stimulated by ginkgo (89). An extract of *Ginkgo biloba* (EGb 761) was preserved with nNOS-positive nerve fibers after cavernous nerve injury in rats (97). EGb inhibits AGE production and down-regulates RAGE expression by reducing oxidative stress (98).

5.4. Morus alba

Leaves of mulberry contain antihyperglycemic and antioxidant compounds (99). In diabetic-ED rats cyanidin-3-O-β-d-glucopyranoside can improve and protect erectile function (100). Mulberry anthocyanin, especially C3R by trapping glyoxal and forming several adducts of mulberry anthocyanin-glyoxal, decreases AGE formation (101).

Table 3. Natural plants for the treatment of glycation-induced ED

Plants	Common name	Function	References
Curcuma longa	Turmeric	It inhibits the AGE effect by trapping methylglyoxal. Water-soluble curcumin enhances erectile function. Decrease glycation burden to minimize the Amadori products and prevent corpus cavernosum from accumulation.	(11, 91, 92)
Epimedium grandiflorum	Horny goat weed, or fairy wings	Upregulation in AGE concentration and downregulation of the NO-cGMP pathway, increase NO synthesis in the penis and enhance SM proliferation.	(18, 95)
Ginkgo biloba	Ginkgo	Increases the NO bioavailability, inhibits AGEs production	(18, 98)
Morus alba	Mulberry	Inhibitory effect on the formation of AGEs, cyanidin-3-O-β-D-glucopyranoside from mulberry is used to protect and improve erectile function.	(100)
Nigella sativa	Black cumin, or black seed	Seed extracts directly relax the blood vessels in the corpus cavernosum, enhancing reproductive performance. Inhibit AGEs formation.	(101, 103, 105)
Panax notoginseng	Chinese ginseng, or notoginseng	For protecting endothelial function in the penile corpus cavernosum, restoring erectile responses and anti-hyperglycaemic	(17, 97)
Pausinystalia yohimbe	Yohimbe	Increased NO synthesis in the penis, enhancing the central sexual impulse.	(18)
Punica granatum	Pomegranate	Improved smooth muscle contraction and intracavernosal blood flow. Its extract or compound shows AGE crosslink cleaving activity, preventing AGE formation.	(112, 113)
Tribulus terrestris	Tribulus	Management of erectile dysfunction shows antiglycation activity and improves low sexual desire	(117, 118, 119)

5.5. Nigella sativa

N. sativa seed extracts affect the penile erection response by directly relaxing the blood vessels of the corpus cavernosum (102). *N. sativa* is used as an antiglycation drug in the treatment of diabetes, and other AGE-related diseases and decreases the formation of AGEs (103). *N. sativa* seed extract inhibits AGEs and Amadori activity by up to 80% (104).

5.6. Panax notoginseng saponins

For 600 years, *Panax notoginseng* (PNS) has been used in China, and this traditional herbal medicine has played an important part in the management of diabetes (107). Studies show a wide range of pharmacological applications, which include anti-inflammatory agents, cardiovascular treatment, anti-cancer, prevention of diabetic complications, and neuroprotection (108). The study shows evidence that expression of eNOS increases due to the activity of the peripheral nervous system (PNS) and controls the accumulation of AGEs and inhibits apoptosis of cells (17). It can also be beneficial for restoring endothelial function in the penile corpus cavernosum by adjusting the NO/cGMP pathway (97). PNS is beneficial for restoring erectile responses and protecting endothelial function, which gives a new therapeutic way for the treatment of patients with diabetic-related ED. Further study is essential to improve the mechanism of the peripheral nervous system in erectile function (17). It has an anti-hyperglycaemic and anti-obese effect and can regulate insulin and leptin (107).

5.7. Pausinystalia yohimbe

Yohimbine is a natural indole alkaloid, which is extracted from a variety of plant barks, such as *Pausinystalia yohimbe,* or from the root of *Rauvolfia serpentina* (108). Yohimbine inhibits human alpha-1 & alpha-2 adrenoceptors for the elevation of central sexual impulse as well as enhances the release of NO from cavernosal endothelial cells. The mechanism of enhancement of sexual function is unclear. It is an α-adrenoceptor antagonist that shows superiority in the treatment of ED (18). 5-10 mg of yohimbine is recommended thrice daily. Headache and anxiety, which may be reported as low or mild, blood pressure, nausea, flushing, increased heart rate, and palpitations are some of its side effects. Positive response rates were found in 34-43% of the most effective ED drugs (49).

5.8. Punica granatum

P. granatum juice helps to decrease nNOS and eNOS levels (109). Pomegranate improved intracavernosal blood flow, erectile activity, relaxation of smooth muscle, and reduction of oxidative products (110). *P. granatum* shows anti-erectile dysfunction properties and is measured by intracavernosal blood flow and penile erection in an arteriogenic ED rabbit model (111).

5.9. Tribulus terrestris

T. terrestris extract improves erectile function (114). *T. terrestris* shows an essential role in treating ED and sexual desire problems. Water extracts of *T. terrestris* show antidiabetic activity (115). *T. terrestris* can protect type 2 DM rats' erectile function by inhibiting cavernosal fibrosis and improving penile endothelial function (116).

6. Conclusion

Treatment of ED has progressed from psychosexual therapy and penile prostheses in the 1970s, through revascularization, and vacuum constriction devices in the 1980s, to transurethral and oral drug therapy in the 1990s. Without a firm understanding of genetics, anatomy, physiology, and the complex interplay of the male reproductive system, the evaluation becomes inefficient and fails to define the etiology. Because of our limited understanding of the male contribution, women endure the health risks of treatments for diseases that may not be there. Gene therapy application in ED represents a new field. In humans, more clinical studies are required in gene therapy, which includes cavernous nerve issues, injury, diabetes, and aging. Natural substances, extracts, and various formulations have been found to be effective in the generation of gonadotropic hormones as well as the activation of antioxidative processes such as lipid peroxidation and glutathione formation. Several natural compounds were also found to be effective in regulating hyperglycemia and apoptotic pathways. However, there are still limitations, such as the paucity of clinical trials in infertility research and the indistinguishability of dosage and use techniques of formulations. The mechanisms of pro-fertility effects are expected to be clarified in future studies, as well as the pharmacological effects of natural compounds for clinical application. As a result, they created a novel avenue that should be investigated further in both diabetic and non-diabetic men.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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None to declare.

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Authors' contributions

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