

REVIEW ARTICLE

Herbs in the treatment of diabetes induced erectile dysfunction

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ABSTRACT

Diabetes mellitus is one of most prevalent degenerative disease. In the Indian scenario, diabetes is emerging as a key health problem in the urban areas. One of the diabetic complications often ignored is erectile dysfunction in men, the prevalence of which is $\geq 50\%$. The pathophysiology of diabetes induced erectile dysfunction (DIED) has various etiological factors involved; hence the treatment is also multimodal. One of the etiological factor for diabetes and its complications is oxidative stress and hence an antidiabetic compound with anti-oxidant property would be beneficial. There are various treatment option available for diabetes and its complications. The management of DIED involves an array of therapies starting with education, counseling, treatment with oral agents (first line and second line agents) to the best alternative i.e., penile prostheses. These treatment options are not without side effects and are also expensive and hence there is need for safe alternatives, which could be in the form of plant based remedies. Such remedies for male sexual dysfunction are aimed not only at the immediate etiological factors of the disease, but also towards improving the hormonal status of the body and relieving the mind from stress. Moreover, an individual with such a problem might not immediately consult a physician, and try self-medication. Thus, in any case one finds plant-based remedies as an easy, economic and safe option. This article proposes few plant-based agents which are/ could be used for treatment of DIED.

Keywords: Aphrodisiacs, steroids, neurotransmitters, medicinal plants

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INTRODUCTION

Sex, a biological imperative of the species, has always held a position of prominence in every time and within every culture nearly without exception. When sexual health encounters a problem it can lead to psychological trauma if not addressed well. Erectile dysfunction often is seen as a result of diseases such as diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular diseases and neurological diseases. Amongst these disorders, diabetes and associated oxidative stress are major contributors for impotency in males. Impotence or erectile dysfunction is defined as inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual

intercourse. An association with diabetes and erectile dysfunction has been documented since 1798 (McCulloch et, 1980). It has been reported that 35-50 percent of men with diabetes experience erectile dysfunction. (Klein et al, 1996; Lewis, 1996 National Institutes of Health (NIH) Erectile Dysfunction, 2004). It is usually present within 10 years of diagnosis. The presence of diabetes mellitus not only increases the risk for ED but also other aspects of sexual dysfunction which include sexual drive, ejaculatory function and sexual satisfaction (Burke et al, 2007).

The pathophysiology for DIED is multifactorial and following are proposed mechanisms Glucose itself and hyperglycemia increases protein glycosylation producing advanced glycation end products (AGEs) (Wolff and Dean, 1987). These might contribute to DIED either by generating free radicals which in turn quench nitric oxide



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(NO) or damage the potassium channels, both of which are required for the cavernosal smooth muscle relaxation (Giuseppe et al, 2006). There is an elevation of endothelins, which are potent vasoconstrictors in the penis, which inhibit the relaxation (Takahsi et al, 1990; Mills et al, 2001). RhoA/ Rho kinase is implicated in decreased production of NO in the penis, which in turn might be responsible for ED (Rees et al, 2002; Bivalacqua et al, 2004). DIED might also be a consequence of neuropathic damage (Costabile, 2003). Impairment of cGMP dependant protein kinase 1 (PKG-1) plays an important role in DIED (Hedland et al, 2000; Chang et al, 2004).

As there are many factors involved in the etiology of DIED, consequently several treatment options are needed for the management of DIED. The first line therapy for DIED is treatment with oral drugs comprising of those which control the blood sugar level, lipid level and blood pressure. Administration of drugs which are directly involved in the treatment of ED include the phosphodiesterase inhibitors, sublingual apomorphine. The second line therapy include the intracavernosal injections or trans urethral suppositories of phentolamine, papaverine and prostaglandin (PGE1), use of vacuum constriction devices, testosterone replacement therapy. The third line therapy and the best alternative when other therapies prove to be ineffective is the use of penile implants (Trove et al, 2011). Although there are several drugs available in the market, there are limitations in their use either due to high cost or side effects like hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc. (Dey, Anoja and Yuan, 2002). In search of first line treatment with better safety and efficacy, research efforts have to be made to find a complete treatment of DIED. The ideal drug to combat DIED is one which involves the NO/cGMP pathway, but a combination of drugs affecting multiple peripheral intracellular targets could also be an option available for treatment.

Medicinal plants are being looked up for the treatment of diabetes and its complications. The WHO has listed 21,000 plants which are used for medicinal purposes around the world. Of these 2500 species are found in India (Seth and Sharma, 2004).

Important/common herbs used in traditional systems of medicine in India and world over are reviewed in detail for their aphrodisiac and antidiabetic effect. These herbs could be promising candidates for exploring their potential in the treatment of DIED, due to their combined effects on erectile dysfunction and diabetes.

Allium sativum

Allicin, a sulfur containing compound is responsible for significant hypoglycemic activity (Sheela and Augusti, 1992). This effect is due to increased hepatic metabolism and increased insulin release from pancreatic beta cells (Bever and Zahnd, 1979). It was later found that S-allyl cysteine sulfoxide (SACS), the precursor of allicin in garlic oil, is the one which stimulates invitro insulin secretion from beta cells (Augusti and Shella, 1996). The plant is also reported to have aphrodisiac properties, one of the study indicates that garlic extract increases the weight of seminal vesicles and epididymides of male rats and also significant-

ly increases the sperm count (Bekairi, Shah and Qureshi, 1990).

Asparagus adscendens

It occurs in the Western Himalayas, Himachal Pradesh and Kumaun, commonly known as safed musli. The tuber is credited with demulcent, nutritive and aphrodisiac properties. It contains steroidal saponins based on stigmasterol and sarsapogenin, asparagin. It may have its activity by reducing seminal weakness and thus curing impotency. The active constituents are reported to have insulinotropic effect, enhancing glucose uptake in adipocytes and inhibiting starch digestion. These effects collectively are beneficial in the treatment of diabetes (Mathews, Flat and Wahab, 2006).

Asparagus racemosus

Commonly known as Shatavari, it contains sitosterol saponins and happens to be an important ingredient in many aphrodisiac tonics (Goyal, Singh and Lal, 2003). It is found to increase the release of insulin, enhance the cellular actions of insulin and inhibit carbohydrate digestion and absorption, thus exhibiting antidiabetic potential (Hannan et al, 2011). One of the study also reports using shatavari for the treatment of diabetic nephropathy (Somania et al, 2012).

Chlorophytum borivilianum

Commonly known as safed musli. The tubers have been traditionally used for various therapeutic applications. It is used as an aphrodisiac, treatment of diabetes and arthritis, curative for prenatal and postnatal problems etc. The roots contain two major constituents (a) Saponins (b) Mucilage. It has been found that this fructo-oligopolysaccharide fraction is effective in treatment of streptozotocin induced diabetes (Narsimhan et al, 2006). Furthermore it is found that the same fraction is also effective in the treatment of sexual dysfunction in hyperglycemic male rats. The probable mechanism behind this effect is improved steroidogenesis and rejuvenation of the entire system that helps in restoring the failing sexual function in diabetes (Thakur et al, 2009).

Commiphora mukul

Guggul is reported to have anti-diabetic activity and it acts as dual activator for PPAR- α and PPAR- γ . (Huang et al, 2009). Guggulsterone, the active principle is reported to possess both hypoglycemic as well as hypolipidemic activity which can help cure type II diabetes (Sharma et al, 2009). It is reported to activate the farnesoid X receptor. This receptor is a hormone nuclear receptor which not only regulates lipid and glucose homeostasis but also influence endothelial function and atherosclerosis. Although no reports directly state the efficacy of guggul in treatment of DIED, it has the farnesoid X receptor agonist activity, which is reported to restore endothelium dependant relaxation in isolated cavernous tissue (Morelli et al, 2011), guggul can be proposed to cure the DIED.

Coleous forskholii

Forskolin isolated from Coleous has vasodilatory effects and has been shown to be effective in the treatment of erectile dysfunction (Mulhall et al, 1997; Lans C, 2007). A

diterpenoid, coleonol isolated from coleous is capable of stimulating the release of glucagon and insulin from islets both *invivo* and *invitro* (Ahmad et al, 1991).

Dioscorea bulbifera

Dioscorea bulbifera containing steroidal saponin based on diosgenin is also believed to act on the seminiferous tubules presumably by exerting a testosterone like effect (Park et al, 2006). Extract prepared from the bulbs of *Dioscorea* is found to inhibit alpha-amylase and alpha-glucosidase, thus helping to manage post prandial hyperglycemia (Ghosh et al, 2011).

Eriosemma kraussianum

Two pyrano-isoflavones isolated from this plant are able to cause relaxation of the corpus cavernosum smooth muscles (Dhlamini, Meyer and Rakuambo, 2002). The same two isoflavones are also reported to have hypoglycaemic effect (Ojewole, Drewes and Khan, 2006; Ojewole and Drewes, 2007). There are no findings that state the use of this drug in DIED, thus it could be an alternative for its treatment.

Eurycoma longifolia

A native to Malaysian peninsula, commonly known as Usitharagai, also found in Indonesia, Thailand, Laos, Vietnam and Cambodia. For centuries it has been used as an aphrodisiac. It contains bitter fatty oil, quassinoids, and various canthine-6-one alkaloids. *E. longifolia* increases the aphrodisiac potency activity in treated animals (Ang, Ikeda and Gan, 2001). This plant also shows some hypoglycaemic activity (Husen, Pihie and Nallappan, 2004).

L-citrulline

L-citrulline occurs naturally in watermelons. The activity of L-citrulline is due to its ability to release NO, which in turn increases the blood flow to the body including the penis. Citrulline has a structural resemblance to arginine, which is known to be beneficial in restricting the diabetic complications (Hoang, Padgham and Meininger, 2013). Another promising candidate for the treatment of DIED is proposed.

Lepidium meyenii found in Andes and Peru, acts on the central nervous system and hence invigorates spermatogenesis on its initial stages (Gustavo et al, 2001). There is only one report which is found to state the hypoglycemic effect of this plant (Eddouks et al, 2005).

Myristica fragrans imparts stimulant and hallucinogenic properties to the main ingredient and prolongs their actions (Tajauddin et al, 2003). *Sida cordifolia*, which contains β -phenethylamines and ephedrine, enhances the release of L-DOPA (Nagashayan et al, 2000). This plant has been ascribed to have rasayana properties in the Ayurvedic texts. Since it has the potential of being an antioxidant it might be helpful in treatment of diabetes induced erectile dysfunction. (Govindrajan, Vijayakumar and Puhspangan-dan, 2005).

Panax ginseng

Commonly known as ginseng it is found in eastern Asia. Over the counter ginseng is available in combinations with various other herbs for use as an aphrodisiac. The roots contains steroidal saponins mainly ginsenosides or panaxo-

sides. *Invivo* and *invitro* studies on corpus cavernosal endothelium of rabbit have shown an aphrodisiac activity (Chen and Lee et al, 1995). Malonyl ginsenosides are effective in lowering glucose levels and improving insulin sensitivity in diabetic animals (William et al, 2006; Young et al, 2012; Liu et al, 2013). Thus combining these effects, it could be proposed for the treatment of DIED.

Ptychopetalum olacoides

Commonly known as marapuama in Brazil, it was used in the form of herbal tea for its strong aphrodisiac properties. The root bark contains saponins, terpenes, flavanoids and phenolic compounds. It is believed to affect the neurotransmitter system and exert its aphrodisiac effect (Antunes et al, 2001; Siqueira et al, 2003).

Quercetin

As mentioned above oxidative stress is one of the etiological factors involved in the pathophysiology of diabetes induced erectile dysfunction. It affects the progression of diabetes due to its antioxidant properties (Vessal, Hemmati and Vasei, 2003; Coskun et al, 2005; Zhang et al, 2011; Jeong et al, 2012)

It is proposed that quercetin could ameliorate erectile dysfunction by inhibiting oxidative stress.

Tinospora cordifolia

The plant is commonly used in rheumatism, urinary disease, dyspepsia, general debility, syphilis, skin diseases, bronchitis, spermatorrhea and impotence. The arabinogalactan polysaccharide isolated from *Tinospora* has been reported to have an anti-oxidant effect in normal animals as well as in diabetic animals. The phytoconstituents of *tinospora* including alkaloids are known to have hypoglycemic effect (Grover, Vats and Rath, 2000; Patel and Mishra, 2011; Patel and Mishra, 2012; Sangeetha, Priya and Vasanthi, 2013). It also reported to be used in treatment of diabetic complications like retinopathy and neuropathy (Agrawal et al, 2012; Nadig et al, 2012). The literature doesn't report its use as an aphrodisiac or as a cure for DIED.

Tribulus terrestris

Commonly known as gokhru, found in sandy soil throughout India, is plentiful in Chennai. In Ayurveda, gokhru either alone or in combination with other herbs is used for curing seminal debility. A recent study has shown that, it exerts its action by improving sexual desire and enhances erection via conversion of protodioscin to dehydroepiandrosterone (Gauthaman, Adaikan and Prasad, 2002; Adaikan et al, 2000) Saponins in gokhru have hypoglycemic effect and hence can be used to lower blood glucose levels. (Li et al, 2002; Amin et al, 2006; Tantawy and Hassanin, 2007).

Trigonella foenum-graceum is found all over India and is used as one of the spices. 4-hydroxyleucine, a novel amino acid from the seeds increases glucose stimulated insulin release. (Sauvaire et al. 1998), administration of the seeds improves glucose metabolism (Khosla, Gupta and Nagpal, 1995) and also reduces hepatic and renal glucose-6-phosphatase and fructose-1,6-biphosphatase activity (Gupta, Raju and Baquer, 1999). The seeds also

have steroidal saponins based on diosgenin and due to its methyl protodioscin and methyl protodeltonin content (Yang et al, 2005); it presumably acts in a manner similar to gokhru in treating erectile dysfunction.

Turnera aphrodisiaca

The Mexicans traditionally used Damiana as an aphrodisiac, tonic and central nervous depressant. The leaves contain volatile oil, glycosides, arbutin as well as β -sitosterol. It might act as an overall tonic that nourishes the libido (Rowland and Tai, 2003; Suresh kumar, Taneja and Sharma, 2005). There are a few reports which state that the plant has some hypoglycemic effects (Perez et al, 1984; Aguilara et al, 1998).

Withania somnifera

Ashwagandha is found throughout the drier parts of India. The active constituents are the alkaloids mainly the hygrine derivatives i.e. withaferine. In Ayurveda and Unani system of medicine the tuber is used as an aphrodisiac, tonic and alterative. It is considered as a rasayana for strength, vigor and rejuvenation. It might have the effect by direct spermatogenic influence on the seminiferous tubules, presumably by exerting a testosterone like effect (Magied, rahman and Harraz, 2001). It is reported that ashwagandha extract and its isolated active components, glycowithanolides are effective in reducing the oxidative damage (Panda and Kar, 1997). Recent studies have also reported to have anti-diabetic effect of ashwagandha (Sharma, Pillai and Khan, 2012; Udayakumar et al, 2010; Udayakumar et al, 2009).

Yohimbine, also referred to as aphrodine or corynine, is another historic aphrodisiac. It is an alkaloid derived from the bark of the yohimbe tree from West Africa. It has been shown to be a powerful sexual stimulant in rats and is a powerful α -2 adrenergic antagonist (Pittler and Ernst, 1998). This has resulted in a great deal of attention for the role of α -2 norepinephrine receptors in sexual arousal.

There is some evidence showing that yohimbine decreases blood glucose levels and increases insulin levels, thus showing anti-diabetic potential (Sandber et al 2012). It can also be recommended in treatment of diabetes induced erectile dysfunction (Tanweer, Fatima, Rahimnadjad, 2010).

Serotonin has generally been viewed as an inhibitory transmitter in the control of sexual arousal. More recently, application of the serotonergic antagonists in rats has led to aphrodisiac effects (Pittler and Ernst, 1998), as it may produce a certain level of relaxation and euphoria.

Dopaminergic stimulation of receptors during sexual response and arousal is located in the forebrain and mid-brain regions. L-dopa has aphrodisiac properties. When L-Dopa was first prescribed in the 1960s and 70s as a treatment for Parkinson's disease, there were a large number of clinical reports of hyper sexuality in patients including eighty-year-old men (Rosen and Ashton, 1993). The seed powder of *Mucuna pruriens* (Kapikacchuu) contains L-DOPA and some other amino acids, mucunine, mucunadine, prurienine, prurieninine. It is used as an aphrodisiac as such and in combination with other herbs (Anantha et al, 1994). Studies have reported to improve

sexual behavior in males suffering from diabetes and thus can be used as sexual invigorator in diabetic states (Bhaskar, Vidhya and Ramya, 2008; Suresh and Prakash, 2012; Suresh et al, 2013). It is also found to be useful in treating other diabetic complications like neuropathy (Grover, Rathi and Vats, 2002).

CONCLUSION

Although, various crude drugs of animal, plant and mineral origin have been used in various cultures for enhancing the sexual performance, very few have been studied for their pharmacological action. Most of these remain scientifically unexplored. A more focused research and understanding is required for validation of these herbs in the treatment of DIED thereby making them globally acceptable. Looking into the plant-based remedies it becomes necessary to establish standards for these herbs and subsequently extract and isolate the active constituents responsible for the aphrodisiac activity. The next thing to follow would be the incorporation of these active constituents in the form of dosage system, which could range from a nutraceutical drink to pharmaceutical dosage form i.e. tablet or capsule. Various herbs in appropriate combinations and with clinical and pre-clinical investigation might result in the development of potent agents in treatment of DIED. There is enormous knowledge hidden in each culture regarding the use of various substances as aphrodisiacs, which need to be explored and substantiated with scientific data.

DECLARATION OF INTEREST

The authors report no declarations of interest.

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