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Unani medicines used in the treatment of diabetes induced erectile dysfunction: A review

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Abstract
Erectile Dysfunction (ED) or Impotence is defined as inability to achieve or maintain an erection sufficient for satisfactory sexual performance. Diabetes mellitus (DM) is one of most prevalent degenerative Polygenic disease affecting app. 69.2 million peoples in India, emerging as a key health problem particularly in Urban areas. Erectile dysfunction is one of the important complications of DM in men affecting more than 50% of them. ED leads to depression, anxiety and can contribute to marital breakdowns where as men are reluctant to seek help for fear embarrassment and become isolated within their relationship. Diabetes induced erectile dysfunction (DIED) has various aetiological factors; hence the treatment is also multimodal. Despite the emphasis on organic ED, pure psychogenic ED occurs, evidence suggests that up to 80 percent of cases have an organic cause. Over exertion, physiological disturbances, lowered level of hormones and strained relationship with partner are the main causes for this disease. One of the etiological factors for diabetes and its complications is oxidative stress and hence an antidiabetic compound with anti-oxidant property would be beneficial. Presently Phosphodiesterase-5 inhibitors are the first line monotherapy for ED, such as Sildenafil and Tadalafil. However, they are not depicted from side effects. In Unani System of medicine, ED is well-defined under the heading of *Zoaf-e-bah* with the synonyms such as *Nuqs-e-Nauoz*, *Zoaf-e-Inaaz*, *Isterqa-e-Qazeeb*. An individual with such a problem might not immediately consult a physician, and try self-medication. Thus, in any case one finds herbal (Unani) remedies as an easy, economic and safe option. This article proposes few Unani Medicines which may be used for treatment of DIED.

Keywords: Unani medicine, DIED, erectile dysfunction, aphrodisiacs, medicinal plants

Introduction
According to the WHO, sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality and not merely the absence of disease, infirmity, or dysfunction.[1] Healthy sexuality is an essential part of human life and it certainly contribute to an improve one's quality of life [1]. Erectile Dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [2]. ED is the inability to get or keep an erection firm enough to have sexual intercourse. It's also sometimes referred to as impotence [3]. There are several classical causes for ED which are - Diabetes Mellitus, Obesity, Hormonal Imbalance, Dyslipidaemia, Heart disease, atherosclerosis, High blood pressure, Parkinson's disease, absence of physical exercise, lower urinary tract infection [4]. Amongst these disorders, diabetes and associated oxidative stress are major contributors for impotency in males. An association with diabetes and erectile dysfunction has been documented since 1798 [5].

According to a report, app. 35%-50% of men with diabetes have erectile dysfunction usually within 10 years of diagnosis [6, 7]. 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 [8].

The pathophysiology for DIED is multifactorial one [9]. Glucose metabolism might contribute to DIED either by generating free radicals which in turn quench nitric oxide (NO) or damage the potassium channels, both of which are required for the cavernosal smooth muscle relaxation [10]. There is an elevation of end othelins, which are potent vasoconstrictors in the penis, which inhibit the relaxation [11]. RhoA/ Rho kinase is implicated in decreased production of NO in the penis, which in turn might be responsible for ED [12]. DIED might also be a consequence of neuropathic damage [13]. Impairment of cGMP dependant protein kinase 1 (PKG-1) plays an important role in DIED [14].

As there are many factors involved in the etiology of DIED, consequently several treatments 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 phoshpodiesterase inhibitors, sublingual apomorphine. The second line therapy include the intracavernosal injections or trans urethral suppositiories of phentolamine, papaverine and prostaglandin (PGE1), use of vaccum 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. 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 [15]. 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. All have serious side effects and higher cost, search of natural supplement from medicinal plants as an aphrodisiac substance is significantly desired.

Several researchers claimed on the basis of preclinical and clinical data, that most of the traditional medicine (plant derivatives, minerals and animal sources) showed beneficial effects in Erectile Dysfunction [16-18].

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 [19].

In Unani literature, *inteshaar-e-zakar* (Penile Erection) is termed as *Nauoz* or *Inaaz* (plural) [20] which is described under the caption of *Amraz-e-Gurda* in the name of *Zauf-e-Bah*. The concept of *Zauf-e-Bah* due to *Nuqs-e-Nauoz* has been mentioned in Unani literatures. Eminent hakims like Ibne Sina in *Al Qanoon Fit Tibb* [21], Ali Bin Abbas Majoosi in *Kamil Al-San't* [22], states that *Nuqs-e-Nauoz* as one of the causes of *Zauf-e-Bah*. Unani system defines erectile dysfunction as *Isterkha e Ala-e-Qazeeb* (Weakness of Penis) - It means, during the act of coitus, the penis neither has any movements nor it gets erected. For normal Erection *Qazeeb' s Asba-e-Majufa* (Smooth Musculature) gets dilated by *Reeh and Rooh-e-Haiwani* (which is associated with arterial blood). When nerves and muscles of this organ get involved (Paralyzed – *Isterq'a*) then it neither dilates nor attains erection. The possible causes of ED are *Zaufe Badan*, Avoidance of sex, *Sue mizaj*, Paralysis of nerves, Specific disease like syphilis cystitis, cystic stones, intestinal worms, rectal disease, or any injury, riding of horses or over indulging in sexual acts / Masturbation [23].

Important/common herbs used in Unani 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.

Khare Khasak (*Tribulus terrestris* L.)

Commonly known as gokhru, found in sandy soil throughout India, is plentiful in Chennai. In Unani, 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 [24]. Saponins in gokhru have hypoglycemic effect and hence can be used to lower blood glucose levels [25].

Aqarqarha (Anacyclus pyrethrum DC.)

The root Aqarqarha plant is mainly used as medicine along with flowers and leaves in Unani system of medicine. Various activities were evaluated like spermatogenic, Anti-diabetic, Immunostimulant, Antidepressant, Anti-convulsant, Memory-enhancing and Anticancer Activity [26]. It is described by Dioscorides, Galen, Avicenna, Avenzoar, Ishaque bin Imran.

A recent study shows that petroleum ether extract of Anacyclus pyrethrum root revealed the improved of sexual potential. Researcher also claimed that penile erection index was significantly increased with reduction in mount latency and intromission latency period [27].

The aqueous extract of A. pyrethrum root increased the weights of body and sex organs, increase sperm count, and reduction of percent of abnormal spermatozoids [28].

Asgandh (Withania somniferous)

Asgandh is found throughout the drier parts of India. The active constituents are the alkaloids mainly the hygrine derivatives i.e. withaferin. In 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 spematogenic influence on the seminiferous tubules, presumably by exerting a testosterone like effect [29]. It is reported that ashwangandha extract and its isolated active components, glycowithanolides are effective in reducing the oxidative damage [30]. Recent studies have also reported to have anti-diabetic effect of ashwagandha [31].

Tarbooz (Citrullus Vulgaris SCHRAD.)

L-citruline 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 [33]. Another promising candidate for the treatment of DIED is proposed.

Sonth (Zingiber Officinale Rosc.)

It is a commonly known as Zanjabeel / Sonth. The root of this plant is used in Unani Medicine. The ethanolic extract of Ginger revealed aphrodisiac activity, stated that the effect may be due to presence of oleoresin compound in ginger. [33] The alcoholic extract of Ginger on the testes of rats against busulfan induced infertility, which showed that *Zingiber offiicinale* increased the semen volume of seminiferous tubules in test group when treated with 100mg/kg of the extract of ginger compared to control group. Sperm count and serum testosterone level was found significantly increased in test group when compared to control group [34].

Satawar (Asparagus racemosus WILLD.)

Commonly known as satawar, it contains sitosterol saponins and happens to be an important ingredient in many aphrodisiac tonics [35]. 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. [36] One of the study also reports using

Asparagus racemosus for the treatment of diabetic nephropathy [37].

Muquil (Commiphora mukul)

Muquil is reported to have anti-diabetic activity and it acts as dual activator for PPAR-α and PPAR-γ [38]. Guggulsterone, the active principle is reported to possess both hypoglycemic as well as hypolipidemic activity which can help cure type II diabetes [39]. 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 muquil in treatment of DIED, it has the farnesoid X receptor agonist activity, which is reported to restore endothelium dependant relaxation in isolated cavernous tissue, muquil can be proposed to cure the DIED.

Lehsan / Garlic (*Allium sativum* L.)

Allicin, a sulphur containing compound is responsible for significant hypoglycemic activity [40]. This effect is due to increased hepatic metabolism and increased insulin release from pancreatic beta cells. It was later found that S-allyl cystein sulfoxide (SACS), the precursor of allicin in garlic oil, is the one which stimulates invitro insulin secretion from beta cells. [40] 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 significantly increases the sperm count [41].

Zombieland (*Dioscorea bulbifera* L.)

Zaminekand containing steroidal saponin based on diosgenin is also believed to act on the seminiferous tubules presumably by exerting a testosterone like effect [42]. Extract prepared from the bulbs of Dioscorea is found to inhibit alpha-amlyase and alphaglucosidase, thus helping to manage post prandial hyperglycemia.

Musli Siyah (*Asparagus adscendens* ROXB.)

It occurs in the Western Himalayas, Himachal Pradesh and Kumaun, commonly known as siya musli. The tuber is credited with demulcent, nutritive and aphrodisiac properties. It contains steroidal saponins based on stigmasterol and sarsapogenin, aspargin. 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 [43].

Bisbasa (Myristica fragrans HOUTT.)

Bisbasa imparts stimulant and hallucinogenic properties to the main ingredient and prolongs their actions [44]. Sida cordifolia, which contains β- phenethylamines and ephedrine, enhances the release of L-DOPA. 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 [45].

Giloy (Timisoara cordifolia WILLD.)

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 [47]. It also reported to be used in treatment of diabetic complications like retinopathy and neuropathy [47]. The literature doesn't report its use as an aphrodisiac or as a cure for DIED.

Methi (*Trigonella foenum*-graceum L.)

It is found all over India and is used as one of the spices. 4-hydroxylecuine, a novel amino acid from the seeds increases glucose stimulated insulin release, administration of the seeds improves glucose metabolism [45] and also reduces hepatic and renal glucose-6-phosphatase and fructose-1,6-biphophatase activity. The seeds also have steroidal saponins based on diosgenin and due to its methyl protodioscin and methyl protodeltonin content [49]; it presumably acts in a manner similar to gokhru in treating erectile dysfunction.

Conclusion

Although, various crude drugs of animal, plant and mineral origin have been used in Unani system 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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