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Review Article

EFFICACY OF *RASON, ASHWAGANDHA* AND *ASHWATHA* IN DIABETIC ERECTILE DYSFUNCTION – A CRITICAL REVIEW

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ABSTRACT

Background: Erectile dysfunction (ED) is a common condition among men with diabetes and it is associated with reduced quality of life among those affected. ED has reported to increase with age, increasing from 5% at 40 years to > 50 % at 75 years of age. The incidence of ED is increasing day by day with the incidence of diabetes and the prevalence of ED is estimated between 35-50%. Erectile Dysfunction (ED); inability to achieve and/or maintaining an erection sufficient to permit satisfactory sexual intercourse, is one of complication associated with diabetes and often ignored. ED problem is 'psycho-organic', because it affects the man as whole. The diabetes and oxidative stress are major contributors for ED. **Objective:** Though there are many medicinal plants shows the antidiabetic and related to beneficial effect in ED. Among those medicinal plants we selected and reviewed *Rason (Allium sativum* Linn.*)*, *Ashwagandha* (*Withania somnifera* Dunal) and *Ashwatha* (*Ficus religiosa* Linn.) To assess and find out the antidiabetic effect and their efficacy in ED. **Research methods and procedure:** In the present study, we collected and compiled (Various research journals) the references regarding previous work done on antidiabetic effect of above mentioned medicinal plants w.s.r. to E.D. **Discussion & Conclusion:** on the basis of our literary review it is concluded that the *Rason (Allium sativum)*, *Ashwagandha* (*Withania somnifera*) and *Ashwatha* (*Ficus religiosa*) are responsible for significant antidiabetic effect with the hypoglycemic property and also exhibit the efficacy in ED due to aphrodisiac properties.

KEYWORDS: *Ashwagandha*, *Ashwatha*, Diabetes, Erectile dysfunction, *Rason*.

INTRODUCTION

The US National Institute of Health define Erectile dysfunction (ED) is the persistent inability of a man to attain or maintain sufficient erection required for satisfactory sexual activity[1]. ED is becoming quite frequent in diabetes patients. There are mainly two types of ED primary, where sexual function is quite normal, or secondary, in which case sexual abnormality occurs after a period of normal sexual activity: in diabetic patients invariably is ED secondary. Erectile dysfunction (ED) is a common condition in diabetic men. Erectile Dysfunction is two or three times more common in Diabetics than in General population. Incidence of Erectile Dysfunction is nearly 65% in men with Diabetes of more than 10 yrs of duration [2]. Erectile Dysfunction has been the most neglected complication of diabetes. ED has reported to increase with age, increasing from 5% at 40 years to > 50 % at 75 years of age. The incidence of ED is increasing day by day with the incidence of diabetes and the prevalence of ED is estimated in India between 35-50% [1]. Diabetic men tend to develop ED 10 to 15 years earlier than non-diabetic men. Where approximately 52% of ED is prevalent in the non diabetic men between the ages of 40 to 70 years, in diabetic men it ranges from 35% to 75% that begins at an earlier age. After 70 years of age, 2/3rd of the general male population is diagnosed with ED. The occurrence of ED in diabetic men between 20-29 years of age is only 9% that rises to 95% by 70 years of age. It was found that erectile dysfunction occurs within 10 years of the onset of diabetes in 50% of diabetic men [3]. The presence of diabetes mellitus not only increases the risk for ED but can other aspects of sexual disorders such as sexual drive, PME (Premature ejaculation), and sexual satisfaction[4]. Diabetic ED is multifactorial in pathophysiology and the mechanism is proposed that glucose itself and hyperglycemia increases protein glycosylation producing advanced glycation end products (AGEs)[5]. Medicinal plants are being looked up for the treatment of diabetes and its complications. Important herbs/medicinal plants are being used traditionally in India for their anti-diabetic and aphrodisiac effect. These herbs/medicinal plants could be promising candidates for exploring their potential in the treatment of diabetic ED, due to their combined effect on diabetes and ED.

The aim of the present review study is to provide an update on the epidemiology, patho-physiology and assess the anti-diabetic effect of *Rason (Allium sativum)*, *Ashwagandha* (*Withania somnifera*) and *Ashwatha* (*Ficus religiosa*) and their efficacy in ED.

MATERIAL AND METHODS

Details of articles, books and internet related to diabetes and ED and efficacy of selected herbs in the management of diabetic ED are reviewed. Older studies were included selectively if relevant and data regarding treatment and result reviewed. Here, an attempt has been

made to gathered those scattered reporting from various published research articles and books related to efficacy of selected herbs in diabetes and ED.

EPIDEMIOLOGY

Diabetes, which is strongly associated with changing life style, is reaching pandemic level. Due to life style and food habit changes are the major cause for the diabetes. Indeed, the world diabetic population is expected to reach 366 million by the year 2030[6]. In India, it is estimated to be 58%, from 51 million people in 2010 to 87 million in 2030[7]. And among these diabetic people, more than 50% have sexual troubles caused by their disease. The incidence of ED is higher in patients taking diabetic treatment.

Etiology and Patho-Physiology of Ed in Diabetes

The patho-physiology of ED in diabetic men is multifactorial and no single cause is reasonable. Diabetes further rises to development of advance glyceted end products (AGEs). Generally, the formation of AGEs is based upon the non enzymatic reaction between glucose and lipoprotein or nucleic acid[8] which leads to decrease thickening, elasticity, increase atherosclerosis and conversion in endothelial function[9].

The relationship between AGEs with diabetic ED is based on generation of free radical oxygen which comes from quenching of NO and oxidative cell damage have major role in relaxation of cavernosum smooth muscle. High levels of effects are particularly seen on the potassium channel which is mainly responsible for subsequent relaxation of cavernosal smooth muscles and intracellular facilitation of the release of calcium. Early development of diabetic ED takes place on damage of potassium channels[10].

Erection is a neurological phenomena and ED can be developed due to dysfunction of pudendal nerve or their terminal branches. Somatic and autonomic nerve dysfunction can be demonstrated in diabetic men who have longer latency somatosensory-evoked potentials of the pudendal nerve and bulb cavernous and urethronal reflexes[11]. Recent researches have shown that the transduction pathway for endothelial involving GTP-binding protein, Rho-kinase, RhoA and its effectors agent might play a role in development of diabetic ED. It is suggested that the RhoA/Rho-kinase pathway interfere ED through decreased production of NO in the penis[12].

Impairment of Cyclic Guanosine Mono Phosphate (cGMP) plays an important role in ED in diabetes. The formation of cGMP does not going to interfere with NO in relaxation of the corpus cavernosum[12] whereas the high level of superoxide radicals present at cavernosal tissue. DIED have decreased level of NO synthase that results into another possible pathways leading to smooth muscle and cavernosal dysfunction[13]. It is also hypothesized that guanylyl cyclase activity impairs in DM by decreased production of cGMP. Furthermore, ineffective endothelial dysfunction rapidly delivers the functional syncytium of the corpora cavernosa that leads to decrease NO and cGMP that involve signicantly in the development of diabetes ED[14]. Elevated HbA_{1c} level and the associated hyperglycemia in men with diabetes have been postulated to decrease NO activity and reduce endothelium-dependent relaxation factors, resulting in an increase risk of ED. HbA_{1c} level greater than 8.1% increase the incidence of ED threefold[15]. It is reported that diabetes have damaging effects on testosterone production which further effect on local endocrine transmitters by impaired LH response to GnRH stimulation of basal normal gonadotropin levels[16].

MEDICIANL PLANTS EXPLORED IN DIABETIC E.D.

Medicinal plants, since time immemorial, have been used in virtually all cultures as a source of medicine. It has been estimated that about 80-85% of population, both in developed and developing countries rely on traditional medicine for their primary health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles[17].

***Rason* (*Allium sativum* Linn.)**

Rason consists of bulb of *Allium sativum* Linn. (Fam. Liliaceae); a perennial bulbous plant, cultivated throughout India as an important condiment crop[18]. Raw cloves of *Allium sativum* Linn. have long been used as dietary supplement for traditional treatment of diabetes. Former is used as stimulant, diuretic and expectorant[19]. It consist volatile oil containing Allyl Disulphide and Diallyl Disulphide. It also contains Allin, Allicin, Mucilage and Albumin[18]. *Allium sativum* Linn. contains many sulphur containing compounds mainly in the form of cysteine derivatives viz. S-allyl cysteine sulphoxides which decompose into a variety of thiosulfinates and polysulfides by the action of enzyme allinase on extraction. Decomposed products are volatile and are present in the oil of garlic. They possess antidiabetic, hypocholesterolemic, fibrinolytic and various other biological actions[20]. A study on allicin, a sulfur containing compound, showed hypoglycemic activity[21] due to increased hepatic metabolism and increased insulin release from pancreatic beta cells[22]. Aqueous homogenate of *Allium sativum* (10ml/kg/day) administrated orally to sucrose fed rabbits (10g/kg/day) in water for two months significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose[23]. Rason is also reported to have aphrodisiac property along with antidiabetic activity. Its cloves are used traditionally to enhance sexual power[24]. A study exhibited that extract of *Allium sativum* increases the weight of seminal vesicles and epididymides of male rates and also significantly increases the sperm count[25]. It is reported that the ability of *Rason* to increase both Nitric Oxide Synthesis (NOS) and the production of one of the essential cofactors- TBH for the enzyme, adds support to the claim that garlic can exert some of its therapeutic properties by increasing NO production in the body[26]. It was reported that *Rason* increase the activity of GTP-Cyclohydrolase-I enzyme, which is responsible for the synthesis of TBH (tetrahydrobioprotein) by GTP[27]. *Rason* increases in NOS activity depending on dose. The vascular endothelium has a primary regulatory role to keep the blood vessels dilated and NO is continuously released by vascular endothelial cells and regulates the blood flow and vasodilaiton. This release of NO appears to be shear stress and tone

dependent and this constitutes a local vascular reflex mechanism to sustain regional blood flow into vascular beds in the presence of intense sympathetic vasoconstriction[28]. It is reported in comparative study of Allium sativum and Sildenafil citrate; a drug to enhance the sexual activities and used in ED in western country, explored the result that Siladenafil citrate increases blood GMP level by inhibiting its degrading enzyme phosphodiesterase-5 (PDE-5), while Allium sativum act by activation of guanalyl cyclase enzyme and thus by increasing production of GMP in body[29].

***Ashwatha* (*Ficus religiosa* Linn.)**

Ficus religiosa Linn, commonly known as the *Ashwath* tree, belongs to the Moraceae family and found throughout India. The bark contains bergenin, leupin-3-one, methyl oleoanolate, lanosterol, β-sitisteryl-Dglucoside, stigmasterol. The bark is altrative, haemostatic, laxative, and bark is used for the treatment of diabetes[30]. A study showed that aqueous extract of *Ficus religiosa* bark was investigated in normal, glucose-loaded hyperglycemic and streptozotocin (STZ)-induced diabetic rats. Oral administration of *Ficus religiosa* bark aq.extract at the doses of 25, 50 and 100 mg/kg was studied in normal, glucose-loaded and STZ diabetic rats. The freshly prepared solutions were orally administered daily for 21 days. The three doses caused significant reduction in blood glucose levels in all the models due to the phyto-costituents given in Table.1. The effect was more pronounced in 50 and 100 mg/kg than 25 mg/kg. *Ficus religiosa* bark aq.extract also showed significant increase in serum insulin, body weight and glycogen content in liver and skeletal muscle of STZ-induced diabetic rats while there was significant reduction in the -levels of serum triglyceride and total cholesterol. *Ficus religiosa* bark aq.extract also showed significant anti lipidperoxidative effect in the pancreas of STZ induced diabetic rats. The results indicate that aqueous extract of *Ficus religiosa* bark possesses significant antidiabetic activity[31]. It was reported that a phytosterolin isolated from *F. religiosa* root bark when given at a dose of 25 mg/kg orally to fasting rabbits produced a maximum fall of the blood sugar level, equivalent to 81% of the tolbutamide standard, after 5-7.5 mg/kg a maximum effect was achieved after 2 hour[32]. Aqueous extract of *F. religiosa* orally decreases the fasting blood glucose. *F. religiosa* modulates the enzymes of antioxidant defense system to combat oxidative stress .As a result glutathione was restored and inhibited the formation of malondialdehyde, proving its anti-diabetic activity along with antioxidant potential[33]. A clinical study carried out of *F. religiosa* root bark, stem bark, fruit and tender leaf buds powder was given to subjects in form of *Kshirpak* methods in diabetic erectile dysfunction for 45 days. In this study it was investigated that 42.86% penile rigidity increase which is highly significant ($P<0.001$), 8.7% improvement in penile erection. *F. religiosa* showed a highly significant in International Index of Erectile Function (IIEF) scoring[34].

***Ashwagandha* (*Withania somnifera* Dunal)**

Withania somnifera Dunal; a small woody shrub, commonly known as Indian ginseng/ *Ashwagandha* , belongs to Solanaceae family, has been an important herb in the *Ayurvedic* and indigenous medical systems for over 3000 years. *Ayurved* indicated it as a general tonic and aphrodisiac agent and it is used in various ailments. The roots of the plant are categorized as *Rasayanas*, which are routed to promote health and longevity by augmenting defense against disease, arresting the ageing process, revitalizing the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and creating a sense of mental well being[35]. *Withania somnifera* has been revealed as an immune stimulator and also an immune regulator in immune inflammation[36]. It is also credited to be hypoglycemic activity[37] in various experimental animal studies. The hypoglycemic activity of ethanolic root extracts of *Withania somnifera* was tested on streptozotocin treated diabetic sprayul rats over a period of three weeks and prominent hypoglycemic activity was reported in lowering blood glucose in type I diabetic model[38]. Hypoglycemic and hypolipidaemic effect of *Withania somnifera* root and leaf extract on Alloxan induced diabetic albino wistar strain rats has also been reported[39]. Antidiabetic activity of purified Withanolides obtained from hydroalcoholic extracts of dried berries was also reported[40]. Similarly, purified Withanolides of *Withania somnifera* revealed significant inhibition of post prandial rise in hypoglycaemia post sucrose load in SDZ induced diabetic rats[41]. In a clinical study it was investigated that 3gm/day root powder of *Withania somnifera* were given to the subjects for one month twice a day and result showed that 12% reduction in blood sugar level[42].

In *Ayurved* the root of *Ashwagandha* is being used as an aphrodisiac and alterative. It is considered as *Rasayan* 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[43]. An animal study showed diabetes was induce by single dose (60mg/kg) of STZ in winstar male rats and orally *withania somnifera* root was given in pelleted food at ratio of 6.25% for 4 weeks. The result showed that root was effective in lowering FSH serum level in somnifera-treated animals compared to controls ($p<0.05$) in both diabetic and non-diabetic groups, whereas progesterone ($p<0.05$), testosterone ($p<0.05$) and LH levels ($p<0.001$) were significantly higher and suggested that *withania somnifera* may have a regulatory effect on diabetes-induced change of the levels of gonadal-hormones[44].

Discussion and Conclusion

Plants have been traditionally used to treat diabetes patients, both insulin dependent & non insulin dependent diabetes all over the world for centuries. They have also been reported to be used in associated conditions of diabetes like diabetic ED, diabetic peripheral neuropathy, diabetic retinopathy etc. Recent scientifically carried out research work have justified the role of herbs in the management of diabetes, however it would be unwarranted to assure that all these plants can be blindly used in diabetic patients. Although there is an increase in the number of patients suffering from diabetic ED during the last decade. Herbs are highly esteemed for millennia as

a rich source of therapeutic agents for prevention and treatment of diabetes and its associated ailments. Hence, I reviewed update information regarding diabetic ED and many herbs traditionally being used in this condition. I selected only three medicinal plants which are widely used for Diabetic ED. On the basis of our reviewed the *Rason (Allium sativum)*, *Ashwagandha* (*Withania somnifera*) and *Ashwatha* (*Ficus religiosa*) is responsible to decreased serum glucose, triglycerides, cholesterol, urea, uric acid, AST and ALT, while increased serum insulin level and showed hypoglycaemic effect attributed mainly to allicin-type compounds and the hypoglycaemic potency of *Allium sativum* has been attributed to the sulphur compounds [di (2-propenyl) disulphide and 2-propenyl propyl disulphide, respectively]. *Withania somnifera* exhibited hypoglycemic effect due to its property to increase the level of serum insulin and activities of catalase, superoxide dismutase and glutathione peroxidase, indicative of its antioxidant property. *Ficus religiosa* have the potent hypoglycemic effects due to β-sitisteryl-Dglucoside; Antidiabetic Phytochemicals. The majority of the experiments confirmed the benefits of these medicinal plants with hypoglycemic effects in the management of diabetes. The mechanism of hypoglycaemic action probably involves direct or indirect stimulation of insulin secretion. *Allium sativum*, *Withania somnifera* and *Ficus religiosa* also described for sexual disability in ancient literature even though *Ayurveda* claimed its *Vajikarn*; to enhance sexual power.

Ashwagangha is an essential constituent in traditional Indian medicine for the treatment of sexual impotence. It is likely that this effect reflects the tonic, restorative and adaptogenic properties. It has been shown that withanolides relax rabbit corpus cavernosum and this effect is mediated by nitric oxide, released from endothelial or neural cells. These endothelial and neurogenic effects of withanosides in inducing relaxation of the corpus cavernosum may account for the aphrodisiac effect of *Ashwagandha*.

It can be concluded that these medicinal plants reduces blood glucose level by the hypoglycemic property and also having a potent aphrodisiac agent and exhibit the efficacy in diabetic ED.

Further investigations or studies on these plants are also needed to find out their mechanism and isolation of newer molecules which will be helpful for the treatment of diabetes and erectile dysfunction. These plants should be subjected to animal and human studies to determine their effectiveness.

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