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Review

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"Drugs Indicated for The Management of *Ziabetus Shakri* (Diabetes Mellitus) in Unani Medicine- An Overview".

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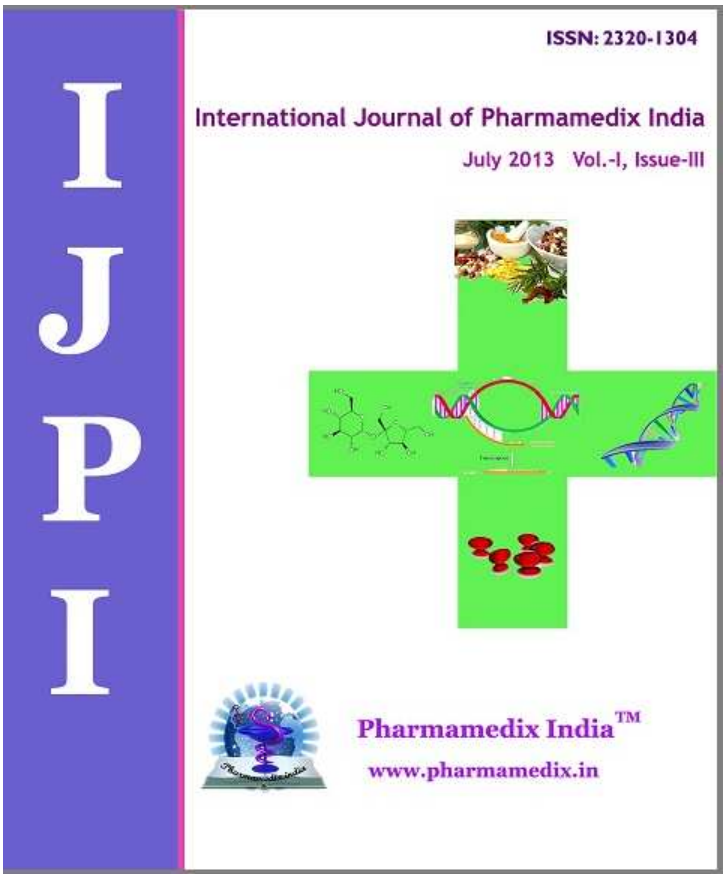

Abstract:

Diabetes Mellitus is a multifactorial metabolic disorder characterized by persistent hyperglycemia, due to absolute or relative deficiency of insulin, causing abnormalities of carbohydrates, proteins & lipid metabolism and significant disturbances of water and electrolytes. According to WHO worldwide prevalence of Diabetes mellitus was estimated to be 371 million in 2012 and it may arise up to 750 million by the year 2030. At first Unani Physicians Galen suspected that this odd illness was caused by a kidney complaint (*Sue mizaj kulya*). Ibn-Sina alone has been credited with two additional discoveries; first the mention of further symptoms besides the triad (polydipsia, polyurea & marasmus) known as antiquity namely physical, mental and sexual weakness and the occurrence of carbuncle and gangrene, secondly the alleged discoveries of sweetness of diabetic urine. Growing diabetic population and the complications associated with Diabetes Mellitus stimulate the search for new drug targets and more efficient drugs with less adverse effect from the natural sources. The present paper deals with brief introduction focusing of common single drugs having hypoglycaemic activity used for the treatment of Diabetes mellitus in unani medicine throughout the Indian Sub Continent.

***Keyword*:** Hypoglycemic drug; Diabetes Mellitus; Diabetic complications; Traditional Medicine; Unani Medicine. Ziabetus shakri.

Introduction:

Diabetes mellitus is a heterogeneous metabolic or endocrine disorder characterized by hyperglycemia, glycosuruia and negative nitrogen balance leading to a number of microvascular (retinopathy, neuropathy & nephropathy) & macrovascular (heart attack, stroke and peripheral vascular disease) complications.[1] In the classical text diabetes classified in two ways, on the presence or absence of sugar in urine viz. *ziabetus shakri* (*ziabetus har*) and *ziabetus sada* (*ziabetus barid*).[2,3] *Ziabetus shakri* is characterized by excessive thirst, excessive urination, excessive appetite, gradual loss of body weight,[3,4] a decrease in sexual function & gangrene is noted as complication of *ziabetus shakri*.[4] Main cause of *Ziabetus Shakri* are *sue Mizaj har* (extreme hot derangement of temperament) of kidney,[5] *hararat,*[4]*sue Mizaj barid* (cold derangement of temperament) of kidney or whole of the body,

zoafe gurda (weakness of kidney), dilatation of ducts & vessels of kidney.[6] In conventional medicine diabetes describe as; Type-1 (IDDM), Tpe-2 (NIDDM) & gestational diabetes mellitus. Type-2 DM is the most common form of diabetes, affecting 90-95 % cases in which the body does not produce enough insulin or properly use it.[7] Diabetes Mellitus is usually associated with advance ageing, high fat diet, and obesity, lack of physical activity or sedentary life style. It is characterized by impaired insulin secretion, peripheral insulin resistance and excessive hepatic glucose production.[8], [9],[10] Currently available therapies for diabetes include insulin and various oral hypoglycemic agents such as, biguanides, glinides & sulphonyl ureas.[11] Use of these drug have a number of serious adverse effect, therefore the search for more effective and safe hypoglycemic agents from natural sources is one of the important areas of innovative analysis.[12] Hypoglycemic activity of medicinal plants is attributed to the presence of flavanoids, terpenoids, polyphenol, carotenoids, coumarins and other constituents reduce the blood glucose level.[13],[14][15] Natural products having hypoglycemic potential which acts through either insulinomimetic or secretogogues properties and also hypoglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissue by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. However, searching for new hypoglycemic drugs from natural source is still attractive, because they contains biomolecules which demonstrate alternative and safe effects on diabetes, out of these some *murakkabat* (compound formulations) and *mufradat* (single drugs) are being used from ancient time and describe in our classical text such as, *Safoofe Ziabetus, Qurs Tabasheer, Safoofe Hindi* & Kachnar (*Bauhina variegata*), Tukhme Jamun (*Eugenia jambolana*), Tukhme Karela (*Momordica charantia*), Satte Gilo (*Tinospora cordifolia*), Tukhme Methi (*Trigonella foenum-graecum*), Kalonji (*Nigella sativa*), Tukhme Hayat (*Withania coagulans*), Chiraita (*Swertia chirayta*), Dammul Akhwain (*Pterocarpus marsupium*), Lahsun (*Allium sativum*), Gurmar Booti (*Gymnemma sylvester*), Tahlab (*Spirulina platensis*) etc.

2.**Few Single Drugs having phytoconstituents and anti-hyperglycemic effect indicated for diabetes Mellitus in Unani system of Medicine**

The main concentration of the review is related to about pharmacological studies performed as anti-hyperglycemic activity of the indigenous plants material (described in unani medicine) and effective bioactive components related to the stimulation of β-cells of the pancreas or its production and its action.

2.1 **Gurmar Booti (*Gymnemma sylvester*)**

Various hypoglycemic principles of *G. sylvestre* isolated from the saponin fraction of the plant are referred as gymnemosides and gymnemic acid. Its triterpene glycosides isolated from plant inhibited glucose utilization in muscles, Gymnemic fractions also inhibit glucose uptake in the intestine. Water extract of *G. sylvester* leaves stimulate insulin secretion from mouse cells and isolated human islets in vitro, without compromising cell viability.[16] Oral administration of water soluble leaves extract of *G. sylvester* at 400 mg/day to 27 insulin dependent diabetes mellitus patients on insulin therapy lowered fasting blood glucose, glycosylated haemoglobin(HbA1c), glycosylated plasma protein and insulin requirements but it remain higher than control.[14] Water soluble *G. sylvester* leaves release insulin probably by causing regeneration of pancreatic β-cells both in vivo & in vitro.[12]

2.2 **Kachnar (*Bauhinia variegate*)**

Crude ethanolic extract of *B. variegate* contain active constituent roseoside have insulinotropic activity in insulin cell line INS-1 and it was found to be dose dependent.[17] Insulin-like proteins from leaves of *B. variegate*, anti-hyperglycemic,[35] anti-hyperlipidaemic,[35] Hepatoprotective activity, [36] antioxidant activity,[37] immunomodulator activity,[38] anti-tumor activity,[39] anti-inflammatory effect.[40]

2.3 **Tukhme Karela (*Momordica charantia*)**

Seeds of *M. charantia* contain phytochemical momordicin, charantin, and a few compounds such as galactose-binding lectin and insulin like protein isolated from various part of this plant have insulin mimetic activity.[12], [18] Polypeptide-p, isolated from seeds, and tissue of *M. charantia* showed potent hypoglycemic effect when administered subcutaneously to gerbits, langurs and human.[19] In a clinical trial, water soluble extract of the fruits of the *M. charantia* significantly reduced blood glucose concentration in the 9 NIDDM diabetes on OGTT (50 gm). Fried *karela* fruits consumed as a daily supplement to the diet produced a small but significant improvement in glucose tolerance in diabetic subjects without any increase in serum insulin levels.[20] *M. charantia* increases the renewal of partial cells in the pancreas or may permit the recovery of partially destroyed cells and stimulates pancreatic insulin secretion.[22]

2.4 **Tukhme Methi (*Trigonella foenum-graecum*)**

Methi seeds contain specific amino acid known as,4-hydroxyisoleucin which posses insulin –stimulating properties.[18] The hypoglycemic effect of *methi* seeds has been demonstrated in experimentally induced diabetic rats, dogs, mice and healthy volunteers both IDDM and NIDDM.[23,24,25] In

a clinical trial administration of *methi* seeds powder (50 mg each with lunch and dinner) in insulin dependent diabetic patients for 10 days shows significant reduction in fasting blood sugar and improved OGTT along with 54% reduction in glycosuria. In addition, it also showed significant hypolipidemic effect.[26] *Methi* seeds acts as anti-oxidant & hypocholesterolemic activity.[27,28]

2.5 **Dammul-akhwain (*Pterocarpus marsupium*)**

Dammul-akhwain commonly known as *vijasar*/Indian kino which contain many chemical constituents like, epicatechin, pterostilbene and marsupin etc. Its active principle, epicatechin has been found to be insulinogenic thus enhancing insulin release and conversion of proinsulin to insulin.[29]An Indian open multicentric study assessing *Vijayasar* in the treatment of newly-diagnosed or untreated NIDDM showed that the extract controlled fasting and post-prandial blood glucose levels in 67 out of 97 patients (69%) by the 12th week at the dose of 2, 3 and 4 gm in 73, 16 and 10% patients, respectively. Four patients were withdrawn from treatment due to excessively high post-prandial blood glucose levels. No significant change was observed in the mean levels of lipids. Other laboratory parameters remained stable during the designated treatment period of 12 week.[30] Pterostilbene (a constituent derived from wood of *P.marsupium*) caused hypoglycemia in dogs (at the dose of 10 mg/kg I.V). Higher dose (20, 30 and 50mg/kg) caused initial hyperglycemia followed by hypoglycaemia lasting for nearly 5 hours.[31] Phenolic constituents such as marsupin and pterostilbene significantly lowered blood glucose level in STZ diabetic rats and the effect was comparable to metformin.[32] One study shows claims its anti-hyperlipidemic activity.[33] Oral administration of the bark decoction (1 gm/100 gm body weight for 10 days) showed a hypoglycemic action in alloxanized diabetic rats.[34]

2.6 **Gilo (*Tinospora cordifolia*)**

Gilo contain many active chemical constituents like- N-formylannonain, N-Methyl-2-pyrrolidone, 11-Hydroxymustakone, cordifolioside A, magnoflorine, tinocordiside and syringing.[44] Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids.[41] Oral administration of 400 mg/kg of aqueous extract of *T. cordifolia* for 15 weeks of treatment showed maximum hypoglycemia of 70.37, 48.81 and 0% in mild (plasma sugar 180 mg/dl), moderate (plasma sugar >280 mg/dl) and severe (plasma sugar >/400 mg/dl) diabetic rats, respectively. Hypoglycemic effect depended upon the functional status of the pancreatic beta cells.[42] anti-

hyperglycemic effect of *T.crispa* extract is probably due to the stimulation of insulin release via modulation of β-cells Ca^{2+} concentration.[43] Immunomodulator activity, [44,45] antioxidant activity,[46] hepatoprotective activity.[47]

2.7 **Tahlab (*Spirulina platensis*)**

Spirulina shows hypoglycemic effect on non-insulin dependent diabetic mellitus,[48,49,50] oral administration of 15 mg/kg spirulina for 45 days in streptozotocin induced diabetic rats significantly reduced the blood sugar level, shows decreased glucose-6-phosphatase activity and increased the hexokinase activity. The decreased activity of glucose-6-phosphatase through pentose phosphate shunt results in a high reduced glutathione to oxidized glutathione ratio which is coupled with conversion of NADPH to NADP.[51]Antioxidant properties of Spirulina were demonstrated as inhibition of lipid peroxidation by its extract,[52] mice fed Spirulina-containing diet showed immuno-enhancing effect,[53] blood lipid-lowering effect of Spirulina has been reported in healthy subjects,[54] anticancer activity,[55] hypocholesterolemic activity,[56] insulin like protein.[57] The United Nations World Food Conference declared Spirulina as "the best for tomorrow," and it is gaining popularity in recent years as a food supplement.[58]

2.8 **Kalonji (*Nigella sativa*)**

N. sativa seed extracts enhance glucose-induced insulin release from rat-isolated Langerhans islets,[59] *N. sativa* supplementation at a dose of 2 gm/day for 12 weeks may improve the dyslipidemia associated with type 2 diabetic patients,[60] The petroleum ether extract of *N. sativa* exerts lipid-lowering and insulin-sensitizing actions in the rat,[61] immunomodulatory activity,[62] *N. sativa* decoction given by intragastric lavage for 9 months was able to correct diabetes and obesity in desert gerbil *Meriones shaw,*[63] antioxidant activity,[64] anticancer activity,[65] hepatoprotective effect of *N. sativa* in rabbit against isoniazid (INH) induced hepatotoxicity.[66]

2.9 **Tukhm Jamun (Syzygium cumini/ *Eugenia jambolina*)**

Aqueous leaf extracts of *S. cumini* inhibits adenosine deaminase activity and reduces glucose levels in hyperglycaemic patients, [67] Oral administration of the aqueous extract of seeds of *S. cumini* (2.5 and 5.0 gm/kg for 6 weeks) showed hypoglycemic (>/ gliben - clamide) and anti-oxidant activity. The hypoglycemic effect was most prominent at the dose of 5.0 gm/kg while no significant effect was observed at 7.5 gm/kg dose. The possible mechanism by which *jamun* seed extract brings about its hypoglycaemic action may be by potentiation of the insulin effect of

plasma by increasing either the pancreatic secretion of insulin from β-cells of islets of Langerhans or its release from the bound form.[68] Oral administration of alcoholic *jamun* seeds extract to diabetic rats at a dose of 100 mg/kg body weight resulted in a significant reduction in blood glucose and urine sugar and lipids in serum and tissues in alloxan diabetic rats, [69] S. cumini seed extracts reduce tissue damage in diabetic rat brain,[70] antioxidant activity,[68] ethanolic extract of *E. jambolana* seed kernel on antioxidant defence systems of plasma and pancreas in streptozotocin-induced diabetes in rats.[71] oral administration of *E. jambolana* Lam. (doses 100, 200 and 400 mg/kg.) significantly prevented carbon tetrachloride induced elevation of serum SGOT, SGPT, ALP, ACP and bilirubin (total and direct) level.[72]

2.10 **Tukhme Khurfa (*Portucca oleracaea*)**

P. oleracaea (Purslane) contains many biologically active compounds, including free oxalic acids, alkaloids, omega-3 fatty acids, coumarins, flavonoids, cardiac glycosides, and anthraquinone glycosides.[73], [74] Crude polysaccharide from purslane on body weight, blood glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride and serum insulin levels were studied in diabetes mellitus mice. Crude polysaccharide treatment (200, 400 mg/kg body weight) for 28 days resulted in a significant decrease in the concentrations of fasting blood glucose, total cholesterol and triglyceride,[75] *P. oleracea* is a rich source of omega-3 fatty acids, which is important in preventing heart attack and strengthening the immune system,[76] antioxidant activity,[77] aqueous extract of *P. oleracea* prevents the TNF-α-induced vascular inflammatory process in the human umbilical vein endothelial cell.[78] The aqueous extract of *P. oleracea* in combination with lycopene (50 mg/kg body weight) acts as hepatoprotective activity in rats against CCl_4 induced hepatotoxicity [79] aquenous extracts of *P. oleracea* have neuroprotective effect against D-galactose induced neurotoxicity [80] aqueous extract of *P. oleracea* ameliorates diabetic nephropathy through suppression of renal fibrosis and inflammation in diabetic mice.[81] *P. oleracea* seeds showed a significant decrease in serum levels of triglycerides, total cholesterol, low density lipoprotein cholesterol, liver alanine, aspartate and gamma glutamyl transaminase, total and direct bilirubin, fasting and post-prandial blood glucose, in type-2 diabetes mellitus patients.[82]

2.11 **Tukhme Kahu (*Lactuca sativa*)**

Decoction of *L. sativa* decrease in the intestinal glucose absorption and shows hypoglycemic effect.[83] Methanolic leaves extract of *L. sativa* shows significant antioxidant potential both in vitro and in vivo.[84] The seed oil is reported to have

sedative, hypnotic, analgesic and anticonvulsant properties[85] *L. sativa* is capable of protecting neurons against glucose/serum deprivation induced cell injury, an *in vitro* model of brain ischemia. *L. sativa* exerts neuro protection and has the potential to be used as a new therapeutic strategy for common neuro degenerative disorders such as stroke [86] it shows anti-inflammatory properties.[87]

Conclusion:

The role of Unani (traditional) Medicine in the management of Diabetes is being appreciated on account of better understanding of mechanism of action of such drugs. Unani physicians have been treating Diabetes Mellitus since ancient times; they have described a number of Unani drugs both single and compound for the management of Diabetes Mellitus. Recently several single herbal drugs mentioned in classical unani literature have been experimentally and clinically evaluated and reported as hypoglycaemic agents. Numerous mechanisms of actions have been proposed for plant extracts. Some hypothesis relates to their effect on the activity of pancreatic β-cells, increase in the inhibitory effect against insulinase enzyme, increase of the insulin sensitivity or the insulin–like activity of plant extracts. However, the scientific study of compound formulation is largely ignored by the scientists and physicians despite the fact that a good number of compound drugs have been described in Unani literature to be effective in Diabetes Mellitus as large number of physicians of Unani medicine are using them successfully since times. This type of review will be of very much help for development of new drugs from natural resources which shows hypoglycemic activity.

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