International Journal of Home Science 2017; 3(2): 305-309

International Journal of Home Science

ISSN: 2395-7476
IJHS 2017; 3(2): 305-309

www.homesciencejournal.com
Received: 17-03-2017
Accepted: 18-04-2017

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Evidence based antidiabetic selected indigenous medicinal plants: A review

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Abstract
About 50% of the Bangladeshi population is at risk of diabetes each year, the majority of people, especially in rural areas, use herbal medicine for diabetes management. Out of a large number of herbal drugs stated to possess anti-diabetic activity in the Unani & Ayurvedic system of medicine. Fact that diabetes can't be cured and it has never been reported that someone had recovered totally from diabetes. The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to mankind health in the world. The traditional medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus. The aim of the present study was to evaluate the evidence based anti-diabetic selected indigenous medicinal plants. Many studies have confirmed the benefits of medicinal plants with hypoglycemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. WHO has pointed out this prevention of diabetes and its complications is not only a major challenge for the future, but essential if health for all is to attain. Therefore, in recent years, considerable attention has been directed towards identification of plants with antidiabetic ability that may be used for human consumption. Further, it emphasizes strongly in this regard the optional and rational uses of traditional and natural indigenous medicines.

Keywords: Medicinal plant, antidiabetic activity, diabetes mellitus

Introduction
Diabetes mellitus is a syndrome, initially characterized by loss of glucose homeostasis resulting from defects in insulin secretion, insulin action both resulting in impaired metabolism of glucose and other energy-yielding fuels such as lipids and proteins [1]. Currently, many countries face large increases in the number of people suffering from diabetes. The World Health Organization (WHO) estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. It is estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years [2]. Diabetes mellitus is a global health crisis, which has been persistently affecting the humanity, irrespective of the socioeconomic profile and geographic location of the population. According to an estimate, one person is detected with diabetes every 5 s somewhere in the world, while someone dies of it every 10 s. [3] Diabetes mellitus has attained a pandemic form. Hence, it is very important to control diabetes and its complications to alleviate the human suffering. Scientists are desperately trying to manage this crippling disorder. Because plants are of enormous medicinal importance, they are being extensively explored for their use against diabetes. Herbal drugs can be quite acceptable as these drugs are known to cause less adverse effects [4]. They are quite popular in developing countries [5]. The increased admiration of herbal medicines for diabetes may be due to the side-effects associated with the conventional antidiabetic drugs [6]. The WHO has also substantiated the utilization of herbal remedies for the management of diabetes [7]. Till date, numerous medicinal plants have been reported to be effective in diabetes, yet plenty of research is still needed to be done. This article focuses on the various plants that could be effective in the treatment of diabetes mellitus. Some reasons like stress, rapid development of cities, and substantial increase in purchase power, lifestyle ease and metro life have lead to health issues and higher number of people suffering from these diseases [8].

The cost of treating diabetes and associated complications exceeds $100 billion per year and complications are far less common and less severe in people who have well controlled blood sugar levels [9]. The treatment of diabetes with synthetic drugs is generally not preferred because of its high cost and side effects for this reason, it is necessary to develop traditional and alternative medicine. Herbal drugs constitute an important part of traditional medicine and literature shows that there are more than 400 plant species showing antidiabetic activity [10].

Anti-diabetic medicinal plants

Gymnema sylvestre

Gymnema sylvestre has long been used as a treatment for diabetes [11-13]. When Gymnema leaf extract is administered to a diabetic patient, there is stimulation of the pancreas by virtue of which there is an increase in insulin release [14]. These compounds have also been found to increase fecal excretion of cholesterol [15]. A number of studies have evaluated the effects of G. sylvestre on blood sugar in animals [16]. In one typical study, diabetic rats received an alcoholic extract of G. sylvestre (100 mg/kg/day) for 1 month [17]. By the second week, the mean blood sugar level was lower among animals receiving the Gymnema extract (74 mg/dL) than among the control group (106 mg/dL). This difference was maintained throughout the study. A blood glucose-lowering effect of similar magnitude produced by tolbutamide has been demonstrated. It should be noted that the doses used would be equivalent to a 7 g dose for a typical man [17]. A more dramatic effect was noted when the extract was administered parenterally to rats [18]. Shanmugasundaram et al. investigated that patients received 200 mg Gymnema powder twice daily in addition to their usual doses of insulin, mean glycosylated hemoglobin (HbA 1c) decreased significantly from baseline (12.8 to 9.5%) at 6 months in a controlled trial of patients with type 1 diabetes [19]. Mozersky reported that 22 patients were given *G. sylvestre* extract along with their oral hypoglycemic drugs [20]. All patients demonstrated improved blood sugar control. Twenty-one out of the twenty-two were able to reduce their oral hypoglycemic drug dosage considerably, and five patients were able to discontinue their oral medication and maintain blood sugar control with the extract alone. The effects of an alcoholic extract of G. sylvestre (GS4) on insulin secretion from islets of Langerhans and several pancreatic β-cell lines were examined by Persaud et al. [21]. GS4 stimulated insulin release from β-cells and from islets in the absence of any other stimulus, and GS4-stimulated insulin secretion was inhibited in the presence of 1mM EGTA. Persaud et al. examined the effects of a novel Gymnema extract on insulin secretion from the MIN6 –cell line and isolated human islets of Langerhans. Insulin secretion from MIN6 cells was stimulated by OSA in a concentration-dependent manner, with low concentrations (0.06- 0.25mg/ml) having no deleterious effects on MIN6 cell viability, while higher concentrations (0.5mg/ml) caused increased Trypan blue uptake [21]. Normal and streptozotocin-induced diabetic rats were treated with either a 50% ethanolic extract of Gymnema leaves (GS3, 20 mg/day/rat), a purified residue of GS3 (GS4, 20 mg/day/rat), or no intervention for up to 95 days [22].

Trigonella foenum

Trigonella foenum graecum leaves are widely used as a vegetable throughout India and have a long history of medicinal use in Unani and Ayurveda medicine. Even though the leaves of this plant are used in diabetes mellitus, there have been no *in vivo* studies to prove its efficacy. Diabetes was induced by streptozotocin (45 mg/kg bw in 0.9% coldsaline).Two doses (250 and 500mg/kg bw) of the extracts were administered in the study. The activity was compared with the reference standard glibenclamide (0.5 mg/kg bw) for various biochemical and histopathological parameters. The activity of the extract in reducing blood glucose, creatinine and urea levels, in enhancing antioxidant enzyme activity and restoring and regenerating islet cells of pancreas was comparable to glibenclamide. The result suggests that ethanol leaf extract of T. foenum graecum possesses significant antidiabetic property [23].

Syzygium cumini

Syzygium cumini (SC) is widely used traditional system of medicine to treat diabetes in India. A compound, mycaminose was isolated from SC seed extract. The isolated compound mycaminose (50 mg/kg) and ethyl acetate [EA] and methanol [ME] extracted compounds of S. cumini seed (200 and 400 mg/kg) was undertaken to evaluate the anti-diabetic activity against streptozotocin (STZ) induced diabetic rates. The compound 'Mycaminose' and ethyl acetate and methanol extracted produced significant ($p<0.05$) reduction in blood glucose level. The standard drug, glibenclamide (1.25 mg/kg) also produced significant ($p<0.05$) reduction in blood glucose level against STZ-induced diabetic rats. The results of this experimental study indicate that isolated compound 'Mycaminose', ethyl acetate and methanol extracts possess anti-diabetic effects against STZ-induced diabetic rats [24].

Capparis spinosa

Diabetes mellitus is the most common metabolic disorders with severe impact on quality of life. Reducing serum glucose levels and normalization of serum lipid is of great clinical importance for treating diabetes. To our knowledge, there are not any evidences about the anti-diabetic action of *Capparis spinosa* root. In the present study the effects of the *C. spinosa* root extract on diabetic metabolic disorders have been studied in experimental diabetes. Rats were divided into six groups: normal control (NC), diabetic control (DC), diabetic rats receiving 0.2, 0.4 g/kg of plant extract or 0.6 mg/kg glibenclamide (groups D0.2, D0.4 or DG respectively). A normal group of rats was also designed to receive 0.2 g/kg of plant extract (N0.2). Rats were rendered diabetic (streptozotocin 60 mg/kg, i.p.) and treated with 0.2, 0.4 g/ kg of plant extract or glibenclamide for four weeks. At the end of the experiment, blood was drawn through heart puncture under deep anesthesia. Weight was measured weekly; glucose levels were measured at the first and fourth week and lipid profiles, insulin and liver enzymes at the end of the study. Glucose levels significantly decreased after treating with plant extract (p=0.003). However, insulin levels did not increase in any treating groups. Plant extract could significantly raise HDL and reduce levels of LDL and liver enzymes (ALT and ALP). These results showed that *C. spinosa* root extract could improve diabetic related metabolic derangement such as hyperglycemia, dyslipidemia, and elevated liver markers in an insulin-independent manner [25].

Catharanthus roseus

Catharanthus roseus is an important Ayurvedic medication in traditional medicine. Due to the great antidiabetic and hyperlipidemic potential of *c. roseus*, we hypothesized that the insulin mimetic effect of ethanolic extract of *C. roseus*

might add to glucose uptake through improvement in the expression of genes of the glucose transporter (GLUT) family messenger RNA (mRNA) in liver streptozotocin **(**STZ)-induced diabetic rats treated by ethanolic extract of c. roseus 100 mg/kg and 200 mg/kg; and one group treated with Metformin (100 mg/kg). After final administration of treatment of 4 weeks, blood samples were collected under fasting conditions, and the body weights (BWs) were measured. Total RNA from liver was extracted with the Qiagen RNEasy Micro kit (GERMANY) as described in the manufacturer's instructions. First-strand complementary DNA (cDNA) was synthesized at 40 °C by priming with oligo-dT12–18 (Invitrogen, USA) and using Super Script II reverse transcriptase according to the protocol provided by the manufacturer (Invitrogen, USA). Real-time polymerase chain reaction (PCR) amplifications for GLUT-4 (gene ID: 25139) were conducted using Light-Cycler 480 (Roche, USA) with the SyBr® I nucleic acid stain (Invitrogen, USA) according to the manufacturer's instructions. Polymerase chain reaction products of β-actin primer gene were used as an internal standard. The proposed study was framed to look at the antidiabetic efficacy of ethanolic extract of *c. roseus* and an expression of GLUT-2 and GLUT-4 gene in streptozotocin induced diabetic wistar rats. The doses were administered orally at a rate of 100 and 200 mg/kg and detrain the glucose transport system in liver for 4 weeks. The observed results showed a good positive correlation between intracellular calcium and insulin release levels in isolated islets of Langerhans. The supplementation of ethanolic extract of *c. roseus* significantly amplified the expression of GLUT gene mRNA by Real Time PCR in liver of diabetic rats. We conclude that the observed antidiabetic effect of *c. roseus* on STZ induced diabetes was a result of complex mechanisms of GLUT gene mRNA expression. The findings are very encouraging and greatly advocate its candidature for the design of a novel herbal drug to cure deadly diabetes [26].

Andrographis paniculata

The chloroform extract of *Andrographis paniculata* roots was tested for its antihyperglycemic activity of alloxan induced diabetic rats using chronic and acute studies. The blood glucose lowering activity was determined after oral administration at doses of 50, 100 and 150 mg/kg body weight in acute study. Whereas in case of chronic study blood glucose, protein, albumin and creatinine levels were estimated after 4 weeks of treatment at the dose of 300 mg/kg. Significant reductions in blood glucose levels were observed in both acute and chronic studies. The extract significanly inhibited the induction of albuminuria, proteinemia and uremia. The study clearly indicated a significant antidiabetic activity with the chloroform extract of A. paniculata roots and supports the traditional usage of the plant by Ayurvedic physicians for the control of diabetes. Also the extract is useful in preventing the incidence of long-term complication, diabetic nephropathy [27].

Tinospora cordifolia

It is found in forests throughout India and is widely used in Ayurveda as tonic, vitalizer and as a remedy for DM and metabolic disorders [28-29]. Oral administration of the water extract of *Tinospora cordifolia* root (2.5, 5 and 7.5 mg/kg) caused a significant reduction in blood glucose, brain lipid level, hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline and lactate dehydrogenase and increase in body weight, total hemoglobin and hepatic hexokinase in alloxanized diabetic rats (150 mg/kg, IP) [30]. Oral administration of 400 mg/kg of aqueous extract of TC for 15 weeks of treatment showed maximum hypoglycemia of 70.37, 48.81 and 0% in mild (plasma sugar /180mg/dl), moderate (plasma sugar / 280mg/dl) and severe (plasma sugar /400mg/dl) diabetic rats, respectively. Hypoglycemic effect depended upon the functional status of the pancreatic beta cells [31].

Emblica officinalis

Amla is a small to medium sized deciduous tree, found in throughout India, Pakistan, Uzbekistan, Sri Lanka, South East Asia, China and Malaysia. It grows about 8-18m height with thin light grey bark, leaves are simple, light green, sub-sessile, closely set along the branchlets looks like pinnate leaves; flowers are greenish yellow; fruits are globose, fleshy, pale yellow with six obscure vertical furrows enclosing six trigonous seeds in two seeded three crustaceous cocci. Amla is highly nutritious and is one of the richest sources of Vitamin-C, amino acids and minerals. It contains several chemical constituents like tannins, alkaloids and phenols. Oral administration of ethanolic extract of seed powder of E. officinalis decreased the blood glucose level and serum cholesterol level in alloxan induced diabetic rats [32].

Hibiscus rosa sinensis

Treatment with the aqueous extract of *H. rosa sinensis* (500 mg kg-1) aerial part reduced the blood glucose level, urea, uric acid and creatinine but increased the activities of insulin, C-peptide, albumin, albumin/globulin ratio and restored all marker enzymes to near control levels of streptozotocin-induced diabetic rats. Thus, it exhibited an antihyperglycemic effect and consequently may alleviate liver and renal damage associated with streptozotocin-induced diabetes mellitus in rats [33].

Terminalia chebula

Terminalia chebula belongs to the family of Combretaceae has been widely used in diabetes in Ayurveda and is widely distributed in India. An herbal formulation containing T. chebula named TRIPHALA is traditional medicine for the treatment of diabetes. Antidiabetic and renoprotective effects of the chloroform extract of T. chebula Retz seeds in streptozotocin-induced diabetic rats was proved. It has potent renoprotective action [34].

Aloe barbidensis

Aloe vera is a cactus like plant with green dagger shaped leaves that are fleshy tapering, spiny and filled with clearly viscous gel. The aqueous extract of Aloe vera has the hypoglycemic property which was given orally at a dose of 150mg/kg of body weight. Whole study was performed on the alloxan induced male albino rats [35-36].

Azadirachta indica

Azadirachta indica is an indigenous plant widely available in India and Burma. Effect of *Azadirachta indica* leaf extract on serotonin inhibition in glucose mediated insulin release in rat pancreas was studied *in vitro* to elucidate the possible mechanism of antihyperglycemic effect [37]. In another study it was shown that hydro alcoholic extracts of this plant has antihyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemi diaphragm. This plant also has anti-bacterial, antimalarial, antifertility,

hepatoprotective and antioxidant effects [38].

Operculina turpethum

Diabetes mellitus (DM) consists of a group of syndromes characterized by hyperglycemia. Prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. *Operculina turpethum*, a medicinal plant widely used in the traditional Ayurveda and Siddha systems of medicine for the treatment of diabetes mellitus. The antidiabetic potential of the methanolic extract of O. turpethum stem (MEOTS) and methanolic extract of O. turpethum root (MEOTR) was evaluated in the Streptozotocin (STZ) - induced type 2 diabetic models. The dose 100 mg/kg of MEOTS and MEOTR were administered to normal, glucose loaded and experimental diabetic rats for 21 days. The significantly ($p< 0.05$) reduction in fasting blood glucose levels were observed in the normal rats at 3 h as well as in the treated diabetic animals at 21 days, thereby justifying the use of the plant in the indigenous system of medicine [39].

Coccinia indica

Coccinia indica is a climbing, herbaceous, branched tropical vine native to tropical Asia, including Bangladesh. Being a part of Indian traditional medicine for ages, it has been widely used in reducing blood sugar among various other uses. Hyperglycemia was induced in overnight fasted healthy adult Wister albino rats by a single intraperitoneal injection of Streptozotocin made in citrate buffer. The diabetic rats in groups received treatment with two different concentrations of the extract, the standard drug and saline. The effectiveness of extract in the maintenance of blood glucose level in both normal and diabetic rats is indicated by significant reduction of the elevated blood sugar level after 10 days of treatment (up to 41.87%) which is comparable to that of standard drug glibenclamide (43.50%) under similar conditions. The results from the experimental studies reflect the efficiency of extract to control blood glucose levels, thereby ascertaining the anti hyperglycaemic activity of methanol extract of *Coccinia indica* and its potential for safe use in the antidiabetic therapy [40].

Momordica charantia

Momordica charantia is reported to possess hypoglycemic activity. Rats were divided into 5groups: normal control, rats received bitter melon, diabetic control, diabetic treated with rosiglitazone (4mg/kg BW), and diabetic received Momordica charantia (300 mg/kg BW). After 4weeks, OGTT, serum insulin, lipid profiles, glycohemoglobin% (HbA1c%), liver enzymes activity and glycogen content, intestinal absorption and diaphragm uptake of glucose and histopathological studies on the pancreas were evaluated. Bitter melon (BM) induced a significant improvement of OGTT and induced a significant decrease in HbA1c% ($p<0.05$), significantly increased insulin release from the pancreas and serum insulin level, increased glucose uptake by rat diaphragm and decreased intestinal glucose absorption ($p<0.05$). BM improved lipid profile. In addition, BM significantly increased liver glycogen content and reduced liver enzyme activity compared to the diabetic control. BM treatment of diabetic rats resulted in significant hypoglycemic and hypolipidemic effects as compared to rosiglitazone ($p<0.05$). Results demonstrated anti-diabetic effects of bitter melon may be through increasing insulin release and serum insulin, increasing glucose uptake by muscles and decreasing intestinal glucose absorption and a hypolipidemic effect and this recommend its therapeutic use in diabetes [41].

Conclusions

Medical plants play an important role in the management of diabetes mellitus especially in developing countries. This review presents the profiles of plants with hypoglycaemic properties, reported in the literature. Out of a large number of herbal drugs stated to possess anti-diabetic activity in the Unani & Ayurvedic system of medicine of Bangladesh, *Gymnema sylvestre, Trigonella foenum, Syzygium cumini, Capparis spinosa, Catharanthus roseus, Andrographis paniculata, Tinospora cordifolia, Emblica officinalis, Hibiscus rosa sinensis, Terminalia chebula, Aloe barbidensis, Azadirachta indica, Coccinia indica, Momordica charantia* were widely used to treat diabetes by the traditional practitioners over many centuries. The present review circumscribes Bangladeshi plants that have been pharmacologically tested and shown to be of some value in Diabetes Mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycaemic plants showed antidiabetic activity with more efficacy than oral hypoglycaemic agents used in clinical therapy.

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