Research Journal of Medicinal Plant

ISSN 1819-3455

Academic Journals Inc.

www.academicjournals.com

Research Journal of Medicinal Plant 5 (4): 352-376, 2011
ISSN 1819-3455 / DOI: 10.3923/rjmp.2011.352.376

Insight into the Hypoglycaemic Effect of Traditional Indian Herbs used in the Treatment of Diabetes

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ABSTRACT

Diabetes mellitus is considered as one of the five leading causes of death in the world. Herbal treatment for diabetes has been a part of traditional medicine for thousands of years. The natural herbs for diabetes treatment focus on lowering blood sugar and reducing the damaging effects of the disease. Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. Diabetes is an important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas. The natural herbs for diabetes treatment focus on lowering blood sugar and reducing the damaging effects of the disease. Herbal supplements for diabetes should be a part of a holistic approach to treatment that addresses proper nutrition, a good exercise program, and continued monitoring of blood glucose levels. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. This review focuses on Indian Herbal plants used in the treatment of diabetes, especially in India.

Key words: Medicinal plant, India, antidiabetic, diabetes, hypoglycaemic

INTRODUCTION

Diabetes mellitus is a heterogeneous metabolic disorder characterized by altered carbohydrate, lipid and protein metabolism (Mutalik *et al*., 2003). It is a common endocrine disorder in which there occur increased food and water intake (Pal *et al*., 2001) and characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). India has today become the diabetic capital of the world with over 20 million diabetics and this number is set to increase to 57 million by 2025 (Sridhar, 2000). This astronomic increase in the prevalence of diabetes has made diabetes a major public health challenge for India.

Herbs for Diabetes treatment are not new. Since ancient times, plants and plant extracts were used to combat diabetes. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these, out of which 150 species are used commercially on a fairly large scale (Zohary and Hopf, 2000). India is the largest producer

of medicinal herbs and is called as botanical garden of the world. The current review focuses on herbs used in the treatment of diabetes mellitus, a major crippling disease in the world leading to huge economic losses. At last even the World Health Organization (WHO) expert committee on diabetes has recommended that traditional medicinal herbs be further investigated. Covered here are medicinal herbs in India that have been confirmed by scientific investigation, which appear to be most effective, relatively non-toxic and have substantial documentation of efficiency.

DIABETES AND SIGNIFICANCE

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 57.2 million by the year 2025. Type I diabetes (Cooke and Plotnick, 2008) (Insulin dependent) is caused due to Insulin insufficiency because of lack of functional beta cells. Patients suffering from type-I are therefore totally dependent on exogenous source of Insulin while patients suffering from Type II diabetes (Elley and Kenealy, 2008) (Insulin independent) are unable to respond to Insulin and can be treated with dietary changes, exercise and medication.

As diabetes is a multifactorial disease leading to several complications, and therefore demands a multiple therapeutic approach. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total lack of insulin, patients are given insulin injections. Whereas in case of those where cells do not respond to insulin many different drugs are developed taking into consideration possible disturbances in carbohydrate-metabolism. For example, to manage post-prandial hyper-glycaemia at digestive level, glucosidase inhibitors such as acarbose, miglitol and voglibose are used. These inhibit degradation of carbohydrates thereby reducing the glucose absorption by the cells. To enhance glucose uptake by peripheral cells biguanide such as metphormine is used. Sulphonylureas like glibenclamide is insulinotropic and works as secretogogue for pancreatic cells. Although, several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc. (Dey *et al*., 2002). Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable antidiabetic and antioxidant therapy.

Medicinal plants are being looked up once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes. *Galega officinalis* is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available. However, experience with guanidine and biguanides prompted the development of metformin. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated.

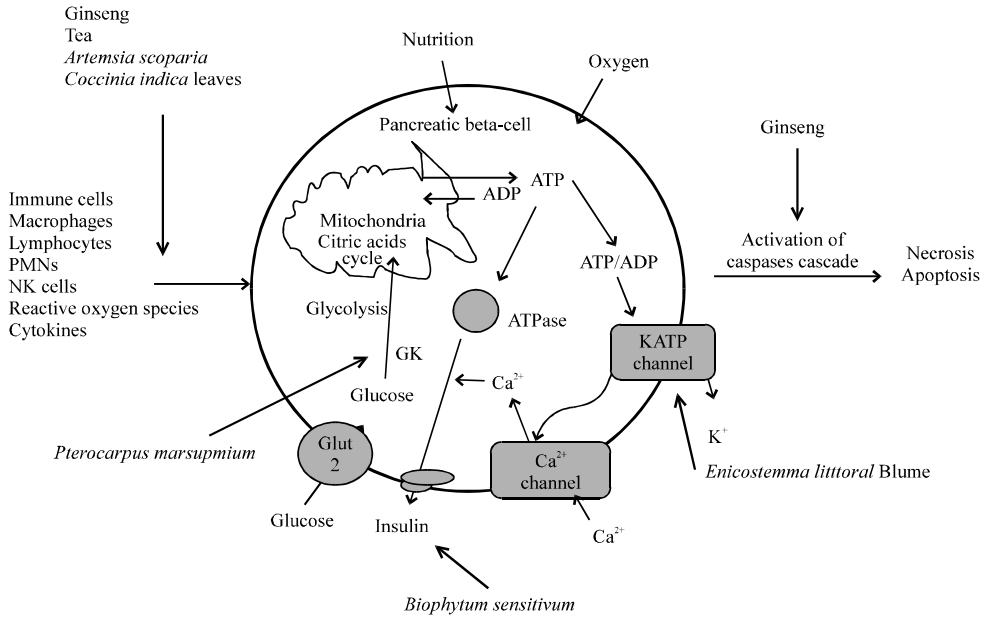

Fig. 1: Insulin secretion and pancreatic-β-cell apoptosis. Glucose is taken up into β-cells via glucose transporters. It is metabolized in glycolysis and Krebs cycle, resulting in an increased ratio of ATP to ADP in the cytoplasm. This closes ATP-sensitive potassium channels (KATP channels), leading to cell membrane depolarization and subsequently opening voltage-gated Ca^{2+} channels. These changes increase free Ca^{2+} concentration ($[Ca^{2+}]i$) in cytoplasm and eventually triggers insulin secretion. In apoptosis, stimuli promotes the release of caspase activators from mitochondria and result in the activation of caspases procedure, by cleaving the effector caspases, which interacts with a variety of cellular proteins, resulting in directly or indirectly the morphological and biochemical characteristics of cell apoptosis. The action sites of hypoglycemia herbs are indicated with a narrow

Conventional diabetic drugs: Western diabetic drugs correct hypoglycemia by supplementing insulin, improving insulin sensitivity, increasing insulin secretion from the pancreas and/or glucose uptake by tissue cells. Under normal conditions, pancreatic β-cells secrete sufficient insulin to maintain blood glucose concentration within a narrow range (72-126 mg dL^{-1}) (Yu *et al*., 2005) (Fig. 1). The insulin stimulation followed by cascade signaling enhances glucose intake, utilization and storage in various tissues (Fig. 2). In diabetic patients, the body loses insulin producing capacity as a result of pancreatic β-cell apoptosis or insulin insensitivity. The cytokines, lipo-toxicity and gluco-toxicity are three major stimuli for β-cell apoptosis (Hui *et al*., 2004) (Fig.1).

There are several types of glucose-lowering drugs (Modi, 2007) (Fig. 3), including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), α-glucosidase inhibitors (miglitol, acarbose). New peptide analogs, such as exenatide, liraglutide and DPP-4 inhibitors, increase GLP-1 serum concentration and slow down the gastric emptying (Hui *et al*., 2005; Garber and Spann, 2008). Most glucose-lowering drugs, however, may have side effects, such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death (Neustadt and Pieczenik, 2008).

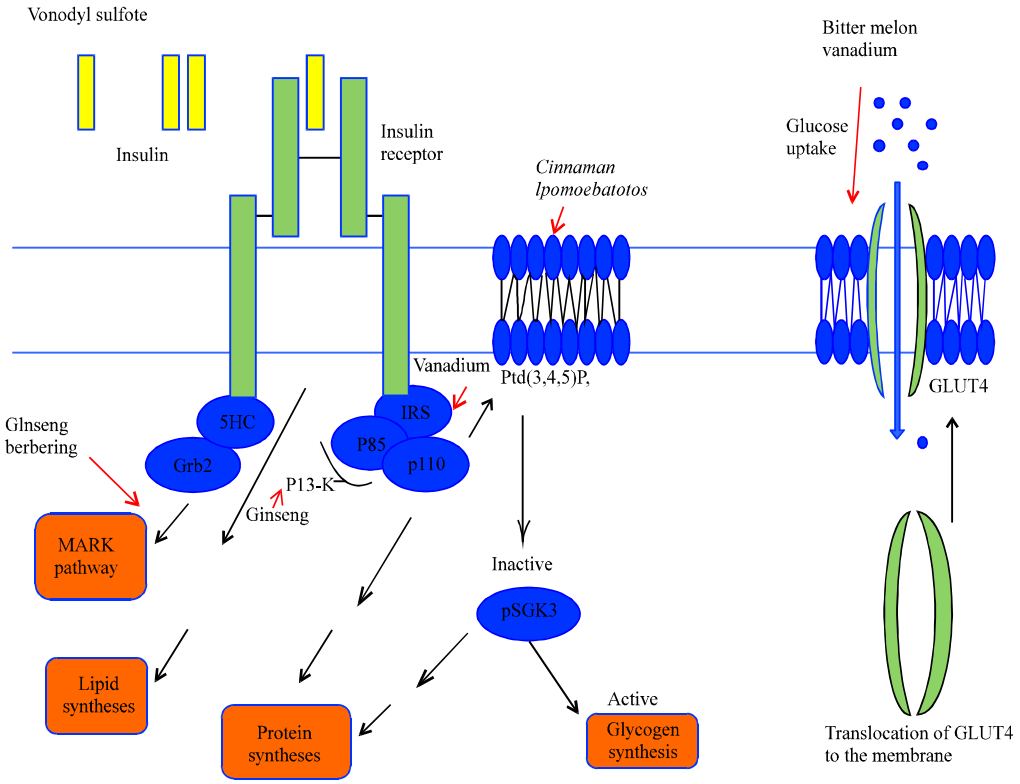

Fig. 2: Insulin signal pathway and insulin insensitive. The inner part of IR reveals a tyrosine kinase activity and coupled with proteins of Src-homology-collagen-like protein (SHC) and multifunctional docking proteins IRS-1 and IRS-2. The interaction of insulin and IR activates its tyrosine activity and phosphorylates the coupled SHC and subsequently activates, in turn, a series of signal proteins, including the growth factor receptor-binding protein 2 (Grb2), and the ras small guanosine 5'-triphosphate-binding protein. The in turn signaling leads to an activation of the MAPK cascade involved in mitogenesis and the open status of a hexose transporter protein (GLUTs), which is located in the cell membrane and is the only pump to take into glucose for cells. The decreased serine/threonine phosphorylation of IR, inactivates hexokinase and glycogen synthase, as well as defects in the phosphorylation of glucose transporter protein (GLUT4) and genetic primary defect in mitochondrial fatty acid oxidation, leading to insulin resistance and an increase of triglyceride synthesis contribute to this insulin insensitivity

Anti-diabetes herbs: Certain herbs may lower blood glucose (Yin *et al*., 2008; Kuriyan *et al*., 2008); however, their test results are subject to several factors. Firstly, each herb contains thousands of components, only a few of which may be therapeutically effective (Angelova *et al*., 2008). Secondly, different parts of an herb have different ingredient profiles. Moreover, different extraction methods may yield different active ingredients (Shan *et al*., 2007). There are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plants form the main ingredients of these formulations. A list of medicinal plants with antidiabetic and related beneficial effects is given in Table 1 (Dixit *et al*., 2006).

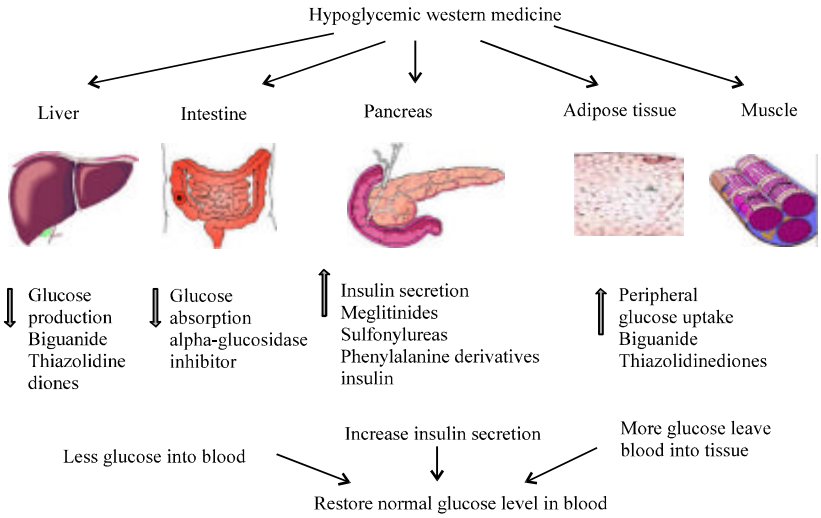

Fig. 3: Action sites of western medicine in diabetes treatment. Hypoglycemic medicines restore euglycemia via several types, including insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), alpha-glucosidase inhibitors (miglitol, acarbose)

***Acacia arabica*: (Babhul):** The plant extract acts as an antidiabetic agent by acting as secretagouge to release insulin. It induces hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of *Acacia arabica* when administered (2,3 and 4 g kg^{-1} b.wt.) to normal rabbits induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells (Wadood *et al*., 1989). Oral administration of cold water extract of *Acacia arabica* bark to diabetic and normal rats at a dose of 400 mg kg^{-1} b.wt. resulted in significant reduction of blood glucose, cholesterol and triglycerides (Yasir *et al*., 2010).

***Aegle marmelos*: (Bengal Quince, Bel or Bilva):** Administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats as compared to control. Along with exhibiting hypoglycemic activity, this extract also prevented peak rise in blood sugar at 1 h in oral glucose tolerance test (Karunanayake *et al*., 1984). A methanolic extract of *Aegle marmelos* was found to reduce blood sugar in alloxan diabetic rats (Sabu and Kuttan, 2004).

***Alchemilla mollis*: (Lady's mantle):** Some modern herbalists recommend lady's mantle as a treatment for diabetes, it may help to prevent circulatory problems in diabetics (Ahad *et al*., 2010).

***Allium cepa*: (onion):** Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. *Allium cepa* is also known to have antioxidant and hypolipidaemic activity. Administration of a sulfur containing amino acid from *Allium cepa*, S-Methyl Cysteine Sulphoxide (SMCS) (200 mg kg^{-1} for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase (Roman-Ramos *et al*., 1995; Kumari *et al*., 1995). When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels (Mathew and Augusti, 1975).

Table 1: Indian medicinal plants with antidiabetic and related beneficial properties

Plant name	Ayurvedic/common name/herbal formulation	Antidiabetic and other beneficial effects in traditional medicine	References
Annona squamosa	Sugar apple	Hypoglycemic and antihyperglycemic activities of ethanolic leaf-extract, Increased plasma insulin level	Kaleem *et al*. (2006) and Gupta *et al*. (2005a, b)
Artemisia pallens	Davana	Hypoglycemic, increases peripheral glucose utilization or inhibits glucose reabsorption	Subramoniam *et al*. (1996)
Areca catechu	Supari	Hypoglycemic	Chempakam (1993)
Beta vulgaris	Chukkander	Increases glucose tolerance in OGTT	Yoshikawa *et al*. (1996)
Boerhavia diffusa	Punarnava	Increase in hexokinase activity, decrease in glucose-6-Phosphatase and fructose bis-phosphatase activity, increase plasma insulin level, antioxidant	Pari and Satheesh (2004a,b) and Satheesh and Pari (2004)
Bombax ceiba	Semul	Hypoglycemic	Saleem *et al*. (1999)
Butea monosperma	Palasa	Antihyperglycemic	Somani *et al*. (2006)
Camellia sinensis	Tea	Anti-hyperglycemic activity, antioxidant	Gomes *et al*. (1995) Devasagayam *et al*. (1996)
Capparis decidua	Karir or Pinju	Hypoglycemic, antioxidant, hypolipidaemic	Agarwal and Chauhan (1988)
Caesalpinia bonducella	Sagarghota, Fevernut	Hypoglycemic, insulin secretagogue, hypolipidemic	Chakrabarti *et al*. (2003) and Sharma *et al*. (1997)
Coccinia indica	Bimb or Kanturi	Hypoglycemic	Kamble *et al*., 1998
Emblica officinalis	Amla, Dhatriphala, aconstituent of herbal formulation, Triphala	Decreases lipid peroxidation, antioxidant, hypoglycemic	Bhattacharya *et al*. (1999), Kumar and Muller (1999 and Devasagayam *et al*. (1995)
Eugenia uniflora	Pitanga	Hypoglycemic, inhibits lipase activity	Arai *et al*. (1999)
Enicostema littorale	Krimihrita	Increase hexokinase activity, Decrease glucose 6-phosphatase and fructose 1,6 bisphosphatase activity. Dose dependent hypoglycemic activity	Maroo *et al*. (2003), Ravi *et al*. (2000) and Augusti *et al*. (1994)
Ficus bengalenesis	Bur	Hypoglycemic, antioxidant	
Gymnema sylvestre	Gudmar or Merasingi	Anti-hyperglycemic effect, hypolipidemic	Chattopadhyay (1999) and Preuss *et al*. (1998)
Hemidesmus indicus	Anantamul	Anti snake venom activity, anti-inflammatory	Alam and Gomes (1998)
Hibiscus rosa-sinesis	Gudhal or Jasson	Initiates insulin release from pancreatic beta cells	Sachadeva and Khemani (1999)
Ipomoea batatas	Ipomoea batatas	Reduces insulin resistance	Kusano and Abe (2000)
Momordica cymbalaria	Kadavanchi	Hypoglycemic, hypolipidemic	Nagaraju (1992) and Rao *et al*. (1999)
Momordica charantia	Bitter gourd	Hypoglycemic	Singh *et al*. (2008)
Murraya koenigii	Curry patta	Hypoglycemic, increases glycogenesis and decreases gluconeogenesis and glycogenolysis	Khan *et al*. (1995)
Musa sapientum	Banana	Antihyperglycemic, antioxidant	Dhanabal *et al*. (2005), Pari and Umamaheswari, (2000) and Pari and Maheswari (1999)

Table 1: Continued

Plant name	Ayurvedic/common name/herbal formulation	Antidiabetic and other beneficial effects in traditional medicine	References
Phaseolus vulgaris	Hulga, white kidney bean	Hypoglycemic, hypolipidemic, inhibit alpha amylase activity, antioxidant. Altered level of insulin receptor and GLUT-4 mRNA in skeletal muscle	Tormo *et al.* (2004), Pari and Venkateswaran (2004) and Knott *et al.* (1992)
Punica granatum	Anar	Antioxidant, anti-hyperglycemic effect	Jafri *et al.* (2000)
Salacia reticulata	Vairi	inhibitotory activity against sucrase, α-glucosidase inhibitor	Yoshikawa *et al.* (1998)
Scoparia dulcis	Sweet broomweed	Insulin-secretagogue activity, antihyperlipidemic, hypoglycemic, antioxidant	Pari and Latha (2005, 2006) and Latha *et al.* (2004)
Swertia chirayita	Chirata	Stimulates insulin release from islets	Saxena *et al.* (1993)
Syzygium alternifolium	Shahajire	Hypoglycemic and antihyperglycemic	Rao and Rao (2001)
Terminalia belerica	Behada, a constituent of Triphala	Antibacterial, hypoglycemic	Sabu and Kuttan (2002)
Terminalia chebula	Hirda	Antibacterial, hypoglycemic	Sabu and Kuttan (2002)
Tinospora crispa		Anti-hyperglycemic, stimulates insulin release from islets	Noor and Ashcroft (1998)
Vinca rosea	Sadabahar	Anti-hyperglycemic	Chattopadhyay *et al.* (1991)
Withania somnifera	Ashvagandha, winter cherry	Hypoglycemic, diuretic and hypocholesterolemic	Adallu and Radhika (2000)

***Allium sativum*: (garlic):** This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity (Sheela and Augusti, 1992). This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect (Bever and Zahnd, 1979). Aqueous homogenate of garlic (10 mL/kg/day) administered orally to sucrose fed rabbits (10 g/kg/day in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls (Zacharias *et al.*, 1980).

S-Allyl Cystein Sulfoxide (SACS), the precursor of allicin and garlic oil, is a sulfur containing amino acid, which controlled lipid peroxidation better than glibenclamide and insulin. It also improved diabetic conditions. SACS also stimulated *in vitro* insulin secretion from beta cells isolated from normal rats (Augusti and Shella, 1996). Apart from this, *Allium sativum* exhibits antimicrobial, anticancer and cardioprotective activities.

***Aloe vera* and *Aloe barbadensis*:** Aloe, a popular houseplant, has a long history as a multipurpose folk remedy. The plant can be separated into two basic products: gel and latex. *Aloe vera* gel is the leaf pulp or mucilage, aloe latex, commonly referred to as aloe juice, is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats (Farida *et al.*, 1987). Treatment of chronic but not single dose of exudates of Aloe barbadensis leaves showed hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also showed hypoglycemic effect in diabetic rats. This action of *Aloe vera* and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells (Ajabnoor, 1990). This plant also has an anti-inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice (Davis and Maro, 1989).

Processed *Aloe vera* gel (PAG) when administered orally for 8 weeks reduced circulating blood glucose concentrations to a normal level in diet-induced obesity mice. The antidiabetic effects of PAG were confirmed by intraperitoneal glucose tolerance testing. PAG lowered blood glucose level by decreasing insulin resistance. The administration of PAG also lowered triacylglyceride levels in liver and plasma. Histological examinations of periepididymal fat pad showed that PAG reduced the average size of adipocytes (Kim *et al*., 2009; Joseph and Raj, 2010a).

***Althaea officinalis* (Marsh Mallow):** Most of the therapeutic ability comes from the large concentration of mucilage and pectin. Pectin is a soluble fiber that keeps the gastrointestinal system running smoothly and helps tame blood sugar (Ahad *et al*., 2010).

***Arctiumlappa* (Burdock roots):** Fresh burdock roots contain phytochemcials called polyacetylenes, which destroy certain bacteria and fungi. Studies revealed that the root extract was found to reduce blood sugar in rats. An extract made from burdock has shown prolonged blood-sugar-lowering effects in animal tests. It works by filling the intestines with fiber, which prevents the absorption of sugars. Burdock's chromium content also helps regulate blood-sugar levels (Ahad *et al*., 2010).

***Azadirachta indica* (Neem):** Hydro alcoholic extracts of this plant showed antihyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm (Chattopadhyay *et al*., 1987a, b). Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects (Biswas *et al*., 2002).

***Berberis lyceum* (Indian Barberry):** *Berberis lyceum* (Berberidaceae) is an important traditional shrub, native to Pakistan and India but also found in other parts of the world. Inhabitants of these areas have been using *Berberis lyceum* for the treatment of diabetes, wounds, broken bones, ulcers and sore eyes. Roots are yellowish in color, rich in alkaloids (berberine, etc.) and other phytochemicals (Bailey and Day, 1989; Leng *et al*., 2004). Gulfraz *et al*. (2007) investigated the antihyperglycemic effects of aqueous and ethanol extracts of *Berberis lyceum* in alloxan induced diabetic and normal rats and concluded that the root extract reduced serum glucose level in normal and diabetic rats, however, the effects of 100 mg kg^{-1} ethanol extracts were more pronounced in alloxan diabetic rats. Furthermore, due to the presence of antihyperglycemic phytochemicals (berberine, etc.) the roots of *Berberis lyceum* have a potential to provide raw materials for pharmaceutical industries (Gulfraz *et al*., 2007).

***Caesalpinia bonducella* (Bonduc):** *Caesalpinia bonducella* is widely distributed throughout the coastal region of India and used ethnically by the tribal people of India for controlling blood sugar. Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II diabetic models. These extracts also increased glycogenesis thereby increasing liver glycogen content (Chakrabarti *et al*., 2003). Two fractions BM 169 and BM 170 B could increase secretion of insulin from isolated islets. The aqueous and 50% ethanolic extracts of Caesalpinia bonducella seeds showed antihyperglycemic and hypolipidemic activities in streptozotocin (STZ)-diabetic rats (Sharma *et al*.,1997). The antihyperglycemic action of the seed extracts may be due to the blocking of glucose absorption. The drug has the potential to act as antidiabetic as well as antihyperlipidemic (Kannur *et al*., 2006).

***Capparis deciduas* (Keekar):** This is found throughout India, especially in dry areas. Hypoglycemic effect was seen in alloxanized rats when the rats were fed with 30% extracts of *Capparis decidua* (*C. decidua*) fruit powder for 3 weeks. This extract also reduced alloxan induced lipid peroxidation significantly in erythrocytes, kidney and heart. *C. decidua* was also found to alter superoxide dismutase and catalase enzyme levels to reduce oxidative stress (Yadav *et al*., 1997). *C. decidua* additionally showed hypolipidaemic activity (Agarwal and Chauhan, 1988). The alcoholic extract of fruit displayed the best hypoglycaemic activity, followed by that of bark and flower (Chahlia, 2009).

***Cinnamomum zeylanicum* (Cinnamon):** It has Insulin-like properties, which able to decrease blood glucose levels as well as triglycerides and cholesterol, all of which are important especially for type II diabetes patients. Just half a teaspoon of Cinnamon into the daily diet of a diabetic can significantly reduce blood glucose levels. Oral administration of ethanolic extract in the doses of 100,150 and 200 mg kg^{-1} b.wt. to white Wistar albino rats significantly reduced their blood sugar level in allxon induced diabetic rats under acute and sub acute studies (Mukul *et al*., 2008).

***Coccinia indica* (Coccinia):** Dried extracts of *Coccinia indica* (*C. indica*) (500 mg kg^{-1} b.wt.) were administered to diabetic patients for 6 weeks. These extracts restored the activities of enzyme lipoprotein lipase (LPL) that was reduced and glucose-6- phosphatase and lactate dehydrogenase, which were raised in untreated diabetics (Kamble *et al*., 1998). Oral administration of 500 mg kg^{-1} of *C. indica* leaves showed significant hypoglycemia in alloxanized diabetic dogs and increased glucose tolerance in normal and diabetic dogs (Ahad *et al*., 2010).

***Costus pictus*:** *Costus pictus* (D.Don) belongs to the family *Costaceae* and it is called as Insulin plant in English, Keu-Hindi, Kottam-Tamil, Kemuka - Sanskrit. It is a vulnerable species, slow growing, perennial herb of tropical and subtropical regions. It is a potent antidiabetic plant and used in folk, ayurvedic and homeopathic systems of medicine (Joshi, 2000). It also used asthma, eye complaints and snake bite and 18 chemical analyzed and identified from leaves of *Costus pictus* (George *et al*., 2007).

The methanol extract of *C. pictus* at a dose of 120 mg kg^{-1} was administered as single dose per day to diabetes-induced rats for a period of 21 days showed significant increases in plasma insulin levels (Jothivel *et al*., 2007). The oral feeding of aqueous leaf solution of this plant in diabetic rats for 28 days at a dosage of 2 g kg^{-1} b.wt. exhibited a significant reduction in fasting blood glucose level and a remarkable increase in serum insulin level (Jayasri *et al*., 2008).

***Emblica officinalis* (Amla):** It is rich in Vitamin C. Amla stimulates the Pancreas to secrete Insulin (Ahad *et al*., 2010). The aqueous extract of *Emblica officinalis* seeds was investigated for its anti-diabetic activity in Streptozotocin induced type 2 diabetes animal models. The dose of 300 mg kg^{-1} of aqueous seed extract in sub- and mild-diabetic animals produced a maximum fall of glucose level in the blood (Shikha *et al*., 2009).

***Eugenia jambolana* (Indian gooseberry, jamun):** In India decoction of kernels of Eugenia jambolana is used as household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Antihyperglycemic effect of aqueous and alcoholic extract as well as lyophilized powder shows reduction in blood glucose level. This varies with different level of

diabetes. In mild diabetes (plasma sugar >180 mg dL^{-1}) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg dL^{-1}) and severe diabetes (plasma sugar >400 mg dL^{-1}) it is reduced to 55.62 and 17.72%, respectively (Sheela and Augusti, 1992). The extract of jamun pulp showed the hypoglycemic activity in streptozotocin induced diabetic mice within 30 min of administration while the seed of the same fruit required 24 h. The oral administration of the extract resulted in increase in serum insulin levels in diabetic rats. Insulin secretion was found to be stimulated on incubation of plant extract with isolated islets of Langerhans from normal as well as diabetic animals. These extracts also inhibited insulinase activity from liver and kidney (Achrekar *et al*., 1991). Administration of the ethanolic extract of kernel of *E. jambolana* at a concentration of 100 mg kg^{-1} of b.wt. significantly decreased the levels of blood glucose, blood urea, and cholesterol, increased glucose tolerance and levels of total proteins and liver glycogen, and decreased the activities of glutamate oxaloacetate transaminase and glutamate pyruvate transaminase in experimental diabetic rats (Ravi *et al*., 2004).

***Ficus racemosa* (Cluster Fig Tree):** *Ficus racemosa* Linn (Moraceae) is an evergreen, moderate to large sized spreading, lactiferous, deciduous tree, without much prominent aerial roots found throughout greater part of India in moist localities and is often cultivated in Indian villages for its edible fruit (Joseph and Raj, 2010b). The ethanol extract (250 mg/kg/day) lowered blood glucose level within 2 weeks in the alloxan diabetic albino rats confirming its hypoglycemic activity (Kar *et al*., 2003; Joseph and Raj, 2010c). β-sistosterol isolated from the stem bark was found to posses potent hypoglycemic activity when compared to other isolated compound (Swain and Downum, 1990; Joseph and Raj, 2010b).

***Ginkgo biloba* (Gingo):** Long used in traditional Chinese medicine, a species that has survived in China for more than 200 million years and now grows throughout the world (Taylor and Thomas, 1993). The extract may prove useful for prevention and treatment of early-stage diabetic neuropathy. It has been shown to prevent diabetic retinopathy. Dosage of the extract standardized to contain 24% ginkgo flavoglycosides is 40-80 mg three times per day (Ahad *et al*., 2010).

***Gymnema sylvestre*:** The indigenous medicinal herb, *Gymnema sylvestre* R. Br. (Family: Asclepiadaceae) is a potential natural alternative to chemical means of blood sugar regulation (Siddhiqui *et al*., 2000). The word Gymnema is derived from a Hindu word Gurmar meaning destroyer of sugar and it is believed that it might neutralize the excess of sugar present in the body in Diabetes mellitus (Keshavamurthy and Yoganarasimhan, 1990).

The plant is reported to be useful in ethno botanical surveys conducted by ethno botanists. It has been documented that the Jungle Irulas inhabitants of Nagari Hills of the North Arcot District, Bombay and Gujarat from India have the habit of chewing a few green leaves of *G. sylvestre* in the morning in order to keep their urine clear and to reduce glycosuria. Bourgeois classes of Bombay and Gujarat also chew fresh leaves for the same effect. In Bombay and Madras, Vaids are known to recommend the leaves in the treatment of furunculosis and madhumeha. The juice obtained from root is used to treat vomiting and in dysentery and plant paste is applied with mother milk to treat mouth ulcer (Kritikar and Basu, 1998; Ekka and Dixit, 2007). Gymnemic acids have antidiabetic, antisweetener and anti-inflammatory activities (Fig. 4).

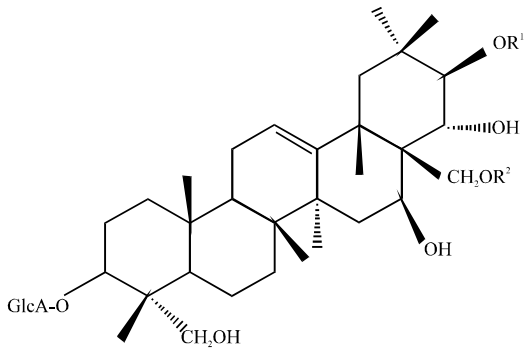

Fig. 4: Structure of gymnemic acid

***Helichry sumitalicum*:** It has been known that by eating ten fully green leaves for every morning for at least three months will prevent diabetes of heredity related (Arulselvan *et al*., 2006).

***Lagerstroemia speciosa* (Banaba):** Banaba possesses the powerful compound corosolic acid and tannins, including lagerstroemin that lends itself to the treatment of diabetes (Burgess, 1987). These ingredients are thought to stimulate glucose uptake and have Insulin-like activity. The latter activity is thought to be secondary to activation of the Insulin receptor tyrosine kinase or the inhibition of tyrosine phosphatase. It is a natural plant Insulin, can be taken orally. The hot water extract of *L. speciosa* leave attributed its prominent hypoglycemic activity on experimental diabetic rats through suppression of gluconeogenesis and stimulation of glucose oxidation using the pentose phosphate pathway (Saha *et al*., 2009).

***Mangifera indica* (Mango):** The leaves of this plant are used as an antidiabetic agent in Nigerian folk medicine, although when aqueous extract given orally did not alter blood glucose level in either normoglycemic or streptozotocin induced diabetic rats. However, antidiabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results indicate that aqueous extract of *Mangifera indica* possess hypoglycemic activity. This may be due to an intestinal reduction of the absorption of glucose (Aderibigbe *et al*., 1999). The ethanol extracts of stem-barks reduced glucose absorption gradually during the whole perfusion period in type 2 diabetic rats (Bhowmilk *et al*., 2009).

***Momordica charantia* (bitter gourd):** *Momordica charantia* (bitter gourd) is one of the many plants considered to have a hypoglycemic effect and many diabetic subjects consume it because of its hypoglycemic effect (Karunanayake *et al*., 1984). Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycemic effect when administered subcutaneously to langurs and humans (Khanna *et al*., 1981). Momordicin (Fig. 5.) is an active compound present in the leaf extract of *M. charantia*.

The ethanolic extracts of *M. charantia* (200 mg kg^{-1}) showed an antihyperglycemic and also hypoglycemic effect in normal and STZ diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6- biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities (Shibib *et al*., 1993). The alcoholic extract of *M. charantia*

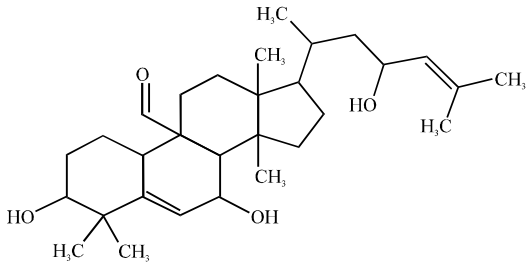

Fig. 5: Structure of momordicin

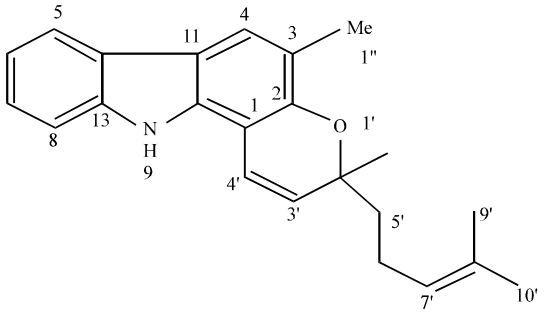

Fig. 6: Structure of mahanimbine

was quite effective in lowering blood sugar levels and islet histopathology also showed improvement. The lowered blood sugar and improvement in islet histology remained as such even after discontinuation of extract feeding for 15 days[56] (Singh *et al*., 2008). The acetone extract of whole fruit powder of *M. charantia* in doses 25,50 and 75 mg/100 g body weight lowered the blood glucose from 13.30 to 50% after 8 to 30 days treatment in alloxan diabetic albino rats, confirming anti hyperglycemic effect of this plant in diabetic animals and humans (Singh and Gupta, 2007).

***Murraya koenigii* (Curry leaves):** The curry tree (*Murraya koenigii*) is a tropical to sub-tropical tree in the family Rutaceae, which is native to India. It is commonly known as Curry Patta (Hindi) is widely used as a spice and condiment in India and other tropical countries.

Various parts of *Murraya koenigii* have been used in traditional or folk medicine for the treatment of rheumatism, traumatic injury and snake bite and it has been reported to have antioxidant, anti-diabetic and anti-dysenteric activities (Kong *et al*., 1986; Keasri *et al*., 2007). *Murraya koenigii* leaves are used traditionally in Indian Ayurvedic system to treat diabetes (Dineshkumar *et al*., 2010).

Mahanimbine (Fig. 6) is a carbazole alkaloid and present in leaves, stem bark and root of *Murraya koenigii*. Most of the carbazole alkaloids have been isolated from taxanonomically related plants of the genus *Murraya, Glycosmic* and *Clausena* from the family Rutaceae (Knolker and Reddy, 2002). The *Murraya* species has richest source of carbazole alkaloids. Further, Carbazole alkaloids has been reported for their various pharmacological activities such as anti-tumor, anti-viral, anti-inflammatory, anti-convulsant, diuretic and anti-oxidant activities (Knolker and Reddy, 2008). Dineshkumar *et al*. (2010) suggested that the mahanimbine has beneficial effect in the management of diabetes associated with abnormal lipid profile and related cardiovascular complications.

The fresh leaves as well as aqueous and methanol extract of *Murraya koenigii* have also found to be hypoglycemic in nature (Khan *et al*., 1995; Rupashree, 1999; Bhat, 1995). Feeding of diet containing various doses of curry leaves (5, 10 and 15%) to normal rats for 7 days as well as mild diabetic (blood glucose levels >175 mg dL^{-1} induced by alloxan 35 mg kg^{-1} IP) and moderate diabetic rats (blood glucose levels >250 mg dL^{-1} induced by STZ 60 mg kg^{-1} IP) for 5 weeks showed varying hypoglycemic and anti-hyperglycemic effect (Yadav *et al*., 2002). Blood glucose levels of diabetic rats treated with aqueous and methanol extracts of *Murraya koenigii* Spreng showed significant reduction ($p<0.05$) as compared to diabetic control groups (Vinuthan *et al*., 2004). The hypoglycaemic effect of curry leaves has been studied in animal models and noninsulin dependent diabetes mellitus (NIDDM) patients (Mani and Iyer, 1990; Grover *et al*., 2003). Oral administration of ethanolic extract of *M. koenigii* at a dose of 200 mg/kg/b.w./day for a period of 30 days significantly decreased the levels of blood glucose, glycosylated hemoglobin, urea, uric acid and creatinine in diabetic treated group of animals (Arulselvan *et al*., 2006).

***Ocimum sanctum* (Holy basil):** It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves of *Ocimum sanctum* showed the significant reduction in blood sugar level in both normal and alloxan induced diabetic rats (Vats *et al*., 2002). Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicated the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats (Rai *et al*., 1997). Oral administration of plant extract (200 mg kg^{-1}) for 30 days led to decrease in the plasma glucose level by approximately 9.06 and 26.4% on 15 and 30 days of the experiment respectively. Renal glycogen content increased 10 fold while skeletal muscle and hepatic glycogen levels decreased by 68 and 75% respectively in diabetic rats as compared to control (Vats *et al*., 2004).

***Panax ginseng* (Ginseng):** It has been shown to enhance the release of Insulin from the pancreas and to increase the number of Insulin receptors. It also has a direct blood sugar-lowering effect. Therapeutic dosage is 100-200 mg daily. The antihyperglycemic and anti-obese effects of Panax ginseng berry extract and its major constituent, ginsenoside Re, in obese diabetic mice and their lean littermates was evaluated (Attele *et al*., 2002).

***Phaseolus vulgaris* (Kidney Bean):** In addition to lowering cholesterol, kidney bean's high fiber content prevents blood sugar levels from rising too rapidly after a meal, making these beans an especially good choice for individuals with diabetes, Insulin resistance or hypoglycemia. It seems that *Phaseolus* preparations should not be considered the first choice in phytopharmaceutical treatment of diabetes or lead structure research. To be effective, fairly high doses of aqueous extracts need to be given. Because of their fiber content and an α-amylase inhibitory effect, beans might be more useful as food components in preventing or ameliorating type 2 diabetes (Helmstadter, 2010).

***Phyllanthus amarus* (bhuiawala):** It is a herb of height up to 60 cm, from family Euphorbiaceae. It is commonly known as Bhuiamala. It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of Phyllanthus amarus was found to have potent antioxidant activity. This extract also reduced the blood sugar in alloxanized diabetic rats (Raphael *et al*., 2002). The plant also shows antiinflammatory, antimutagenic, anticarcinogenic, antidiarrhoeal activity.

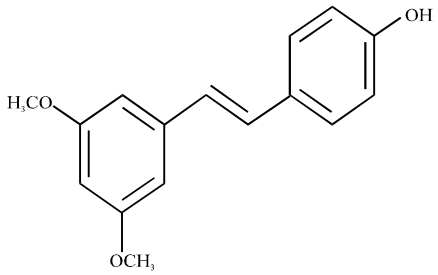

Fig. 7: Structure of pterostilbene

***Plantago ovata* (Ispaghula):** It can be taken in the form of seeds/husk (Freitas *et al*., 2002). In case of diabetics, it controls blood sugar by inhibiting the excessive absorption of sugar from the intestine.

***Prunus dulcis* (Almond):** The fixed Oil of Almonds is extracted from both Bitter and Sweet Almonds (Singh, 2002). They have a special dietary value (containing about 20% of proteins); they contain practically no starch, and are therefore often made into flour for cakes and biscuits for patients suffering from diabetes.

***Pterocarpus marsupium* (Indian Kino):** It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene (Fig. 7), a constituent derived from wood of this plant caused hypoglycemia in dogs (Haranath *et al*., 1958; Joglekar *et al*., 1959) showed that the hypoglycemic activity of this extract is because of presence of tannates in the extract. Flavonoid fraction from Pterocarpus marsupium has been shown to cause pancreatic beta cell regranulation (Chakravarty *et al*., 1980). Marsupin, pterosupin and liquiritigenin obtained from this plant showed antihyperlipidemic activity (Jahromi and Ray, 1993). (-)Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin *in vitro*. Like insulin, (-)epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose-dependent manner (Ahmad *et al*., 1989). The role of *Pterocarpus marsupium* as anti-diabetic has been very well established (Devgun *et al*., 2009). The antidiabetic activity of various subfractions of the alcohol extract of the bark of *Pterocarpus marsupium* Roxb. was evaluated in alloxan-induced diabetic rats (Dhanabal *et al*., 2006).

***Stevia rebaudiana* (Stevia):** Steviosides,(Fig. 8) the principle sugar molecule of Stevia, which is 400 times sweeter than Sucrose, neither absorbed nor metabolized in digestive processes (Parsons and Cuthbertson, 2001). As a result, the Steviosides, molecules pass unchanged through the human gastrointestinal tract and are not absorbed into the blood, producing no calories.

***Syzygium jambolanum* (Jambul Seeds):** Practitioners of ayurvedic medicine report that jambul fruit pulp lowers blood-sugar levels in approximately thirty minutes, while jambul seed lowers blood-sugar levels (Matsui *et al*., 1996) in about twenty-four hours. The maximum hypoglycemic effect of the herb requires ten days of treatment. This Ayurvedic herb has long been used to reduce the level of sugar in the blood and urine. Over a period of several weeks it can diminish the thirst associated with diabetes and decrease the quantity of urine output, and in some cases can lower

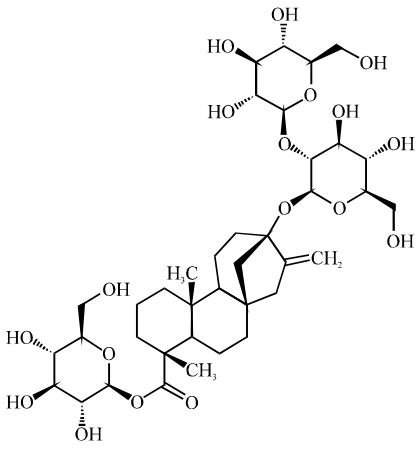

Fig. 8: Structure of steviosides

the need for medical Insulin. The anti-diabetic potential of *Syzygium jambolanum* fruit was studied by analyzing the effect of its crude and fractions on key glucose transport mediators such as IRTK, GLUT4, PI3K and PPAR (Rajasekar and Kirubanandan, 2010).

***Trigonella foenum graecum* (fenugreek):** It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans (Sauvaire *et al*., 1998). Oral administration of 2 and 8 g kg^{-1} of plant extract produced dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats (Gupta *et al*., 1999). Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose -1,6-biphosphatase activity (Ravikumar and Anuradha, 1999). This plant also shows antioxidant activity (Dixit *et al*., 2005; Stanely *et al*., 2003). Recently the antidiabetic activity of Fenugreek seeds were investigated clinically (Ismail, 2009).

***Tinospora cordifolia* (Guduchi):** It is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of *Tinospora cordifolia* (*T. cordifolia*) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight (Prince and Menon, 2001). *T. cordifolia* is widely used in Indian ayurvedic medicine for treating diabetes mellitus (Prince and Menon, 1999; Mathew and Kuttan, 1997). Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg kg^{-1} could elicit significant antihyperglycemic effect in different animal models, its effect was equivalent to only one unit/kg of insulin (Khosla *et al*., 1995). It is reported that the daily administration of either alcoholic or aqueous extract of *T. cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents (Gupta *et al*., 1967). Oral administration of an aqueous *T. cordifolia* root extract and

various extracts (hexane, ethyl acetate and methanol) of stem to alloxan and streptozotocin induced diabetic rats caused a significant reduction in blood glucose level (Stanely *et al*., 2000; Rajalakshmi *et al*., 2009).

***Vaccinium myrtillus* (Blue Berry):** Blue berry is a natural source of lowering blood sugar levels (Zohary and Hopf, 2000). Results have shown the leaves have an active ingredient with a remarkable ability to get rid the body of excessive sugar in the blood.

Other principal Anti-diabetic herbs in common use: Cashew leaves (*Anacardium occidentale*), Madagascar periwinkle leaves (*Catharanthus roseus*), Cumin seed (*Cuminum cyminum*), Goat's Rue seeds (*Galega officinalis*), Gymnema leaves (*Gymnema sylvestre*), Olive leaves (*Olea europaea),* Devil's Club root bark (*Oplopanaxhorridum*), Prickly Pear stems and fruit (*Opuntia* sps), Dandelion plant (*Taraxacum officinale*), Stinging Nettle plant (*Urtica dioica*), Bilberry leaves (*Vaccinium myrtillus*). Celery seed (*Apium graveolens*), Bupleurum (*Bupleurum falcatum*), Gotu kola (*Centella asiatica*), Rosemary (*Rosmarinus officinalis*) (Ahad *et al*., 2010).

CONCLUSIONS

Diabetes has become a global epidemic. Modern medicines, despite offering a variety of effective treatment options, can have several adverse effects. From ancient times, some of the herbal preparations have been used in the treatment of diabetes. Mechanisms such as the stimulating or regenerating effect on beta cells or extra pancreatic effects are proposed for the hypoglycemic action of these herbs.

All the plants discussed in this review have exhibited significant clinical and pharmacological activity. The potency of herbal plants is significant and they have negligible side effects than the synthetic antidiabetic drugs. There is increasing demand by patients to use the natural products with antidiabetic activity. In recent times there has been renewed interest in the plant remedies. Plants hold definite promises in the management of Diabetes mellitus. Isolation and identification of active constituents from these plants, preparation of standardized dose and dosage regimen can play a significant role in improving the hypoglycaemic action.

Major hindrance in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety. Here is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation and developing various animal models for toxicity and safety evaluation. It is also important to establish the active components from these plant extracts.

ACKNOWLEDGMENT

The authors gratefully acknowledged to our Malankara Catholic College Correspondent Fr. Prem Kumar (M.S.W) given encouragement and support for preparation of this manuscript. We wish to express our sincere thanks to Dr. Sujatha (ICBM), Mr. K. Suresh and the research scholars in the Interdisciplinary Research centre for updated article collection and all the efficient supports of this review preparation.

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