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Medicinal Plants with Antidiabetic Potential - A Review

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Abstract: Since ancient times, plants have been an exemplary source of medicine. Ayurveda and other Indian literature mentioned the use of plants in treatment of various human ailments. Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. Oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management of the disease but there is growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agents. Herbal medicines have been the highly esteemed source of medicine throughout human history. Some of these herbal plants and their active chemical constituents which have a role in the management of diabetes mellitus are compiled here and discussed in this review.

Key words: Diabetes mellitus · Medicinal plants · Antidiabetic · Insulin

INTRODUCTION

Diabetes mellitus is one of the common metabolic disorders and 2.8% of the population suffers from this disease throughout the world and it may cross 5.4% by the year 2025. In India, the prevalence rate of diabetes is estimated to be 1-5% [1-3]. Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipedemia, hyperaminoacidemia and hypoinsulinaemia it leads to decrease in both insulin secretion and insulin action [4]. It is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin [5] leads to inherited and/or acquired deficiency in the production of insulin by the pancreas or by the ineffectiveness of the insulin produced. It results either from inadequate secretion of hormone insulin, an inadequate response of target cells to insulin or a combination of these factors. This disease requires medical diagnosis, treatment and changes in life style. The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity. There is a growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agents (therapeutic agent) for the treatment of diabetes mellitus. So the traditional herbal medicines are mainly used which are obtained from plants, it plays important role in the management of diabetes mellitus [6]. In recent years, herbal medicines have started to gain importance as a source of hypoglycemic agents. More than The ethnobotanical information reports about 1000 plants that may possess antidiabetic potential however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. The present review circumscribes plants that have been pharmacologically tested and shown to be of some value in diabetes mellitus.

Plants with Anti-Diabetic Potential

***Abelmoschus moschatus* (Malvaceae):** It is an aromatic medicinal plant, which is native to India. Myricelin, an active principle of A. moschatus, improves insulin sensitivity through increased post-receptor insulin signaling mediated by enhancements in IRS-1-associated PI3-kinase and GLUT 4 activity in muscles of obese Zucker rats. Myricetin might be used as a model substance for the development of antidiabetic compounds [7].

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***Acacia arabica* or *nilotica* (Mimosaceae):** It occurs in wild throughout India and is also cultivated. Feeding of 94% seed diet to normal rats showed significant hypoglycemic effect versus controls. However, the same diet failed to show any hypoglycemic effect in alloxanized rats (175 mg/kg SC) indicating that plant acts through release of insulin. Powdered seeds of *Acacia arabica* administered in doses of 2, 3 and 4 gm/kg body weight exerted a significant (PB/0.05) hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic beta cells. No acute oxicity and behavioral changes were observed at these doses [8]. Powdered seeds of *A. arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits induces hypoglycemic effect by initiating release of insulin from pancreatic beta cells.

***Achyranthes aspera* (Amaranthaceae):** It is distributed throughout the tropical world. Oral administration of *A. aspera* powder produces a significant dose-related hypoglycemic effect in normal as well as in diabetic rabbits. The water and methanol extracts also decreases blood glucose levels in normal and alloxan diabetic rabbits. The acute toxicity study in rabbits does not reveal any adverse or side effects of this folk medicine at dosages up to 8 g/kg orally. The plant could act by providing certain necessary elements like calcium, zinc, magnesium, manganese and copper to the beta-cells [9].

***Achyrocline satureioides* (Asteraceae):** It is a medicinal plant symbol of Rio Grande does Sul state in Brazil. A new prenylated dibenzofuran, achyrofuran, a compound derived from *A. satureioides* significantly lowered blood glucose levels when administered orally at 20 mg/kg q.d. The aqueous extract of the aerial parts of *A. satureioides* administered before bromobenzene (BB), at the dose of 300mg/kg, inhibited the increase of liver ALT and AST, whereas the BB-induced liver shows increase of thiobarbituric acid reacting substances (TBARS) content. Also it significantly increases the depleted levels of liver glutathione. In addition, at the same dose, a significant increase in the bile flow of rats was found. The results obtained with the aqueous extract of *A. satureioides* support its use in popular medicine as a hepatoprotective and digestive agent and the effects might be mediated through the antioxidant and choleretic activities [10].

***Aegle marmelose* (Rutaceae):** A species of tree native to India, it is present throughout Southeast Asia as a naturalized species. A significant decrease in liver glycogen of diabetic rats was brought to almost the normal level by the leaf extract and it also decreases the blood urea and serum cholesterol. It is a medium sized, armed deciduous tree found wild, especially in dry forests and is also cultivated throughout India. Oral administration of aqueous decoction of *Aegle marmelose* root bark (1 ml/100 gm) showed hypoglycemic effect which was maximum (44%) at 3 h in normal fasted rats. In addition, the same extract completely prevented peak rise of blood sugar at 1 h in OGTT. The hypoglycemic activity was reduced upon storage of extract [11]. Aqueous extract of the leaves (1 gm/kg for 30 days) significantly controlled blood glucose, urea, body weight, liver glycogen and serum cholesterol of alloxanized (60 mg/kg IV) rats as compared to controls and this effect was similar to insulin treatment. When fed as aqueous leaf extract (1 gm/kg/day) to STZ (45 mg/kg IV) diabetic rats for 2 weeks, it decreased malate dehydrogenase levels (an enzyme known to increase in diabetes) in comparison to diabetic controls. The extract was equi-effective in comparison to insulin in restoring blood glucose and body weight to normal levels. Aqueous leaf extract administered orally for 28 days also normalized STZ (45 mg/kg body weight) induced histopathological alterations in the pancreatic and kidney tissues of rats [12].

***Agrimony eupatoria* (Rosaceae):** Agrimony, when incorporated into the diet (62.5 g/kg) and drinking water (2.5 g/L) counters the weight loss, polydipsia, hyperphagia and hyperglycemia of STZ-diabetic mice. Aqueous extract (1mg/mL) stimulates insulin secretion from the BRIN-BDII pancreatic B-cell line, 2-deoxy-glucose transport, glucose oxidation and incorporation of glucose into glycogen in mouse abdominal muscle comparable with 0.1iM-insulin. These results demonstrate the presence of antihyperglycemic, insulin-releasing and insulin-like activity in *A. eupatoria* [13].

***Allium cepa* (Alliaceae):** *Allium cepa* (Onion) is known only in cultivation but related wild species occur in Central Asia. Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. *A. cepa* also known to have antioxidant and hypolipidemic activity. Administration of a sulfur containing amino acid, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues. It normalizes the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase [14,15].

When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels. Petroleum ether insoluble fraction of the ether extract of dried onion powder (100 mg/kg) given orally for 7 days to alloxanized (180 mg/kg) diabetic rabbits caused a significant anti-hyperglycemic effect. Oral administration of 250 mg/kg of ethanol, petroleum, chloroform and acetone extract of powder dried onion showed maximal reduction of 18.57, 8.35, 3.0 and 3.20% in fasting blood glucose of alloxanized (150 mg/kg IP) diabetic rabbit. In a preliminary study of seven different fractions obtained from onion bulb, only petroleum ether and chloroform extracts significantly lowered blood sugar in OGTT (2 gm/kg) in rabbits [16]. Feeding of diet containing 3% freeze-dried onion powder for 8 weeks produced a significant hypoglycemia along with partial reversion of abnormal plasma albumin, urea, creatinine and inorganic phosphorus in STZ diabetic albino rats.

***Allium sativum* (Alliaceae):** It is a perennial herb cultivated throughout India and is commonly used as a food ingredient. Oral administration of 0.25 gm/kg of ethanol, petroleum ether, ethyl ether extract of *Allium sativum* causes 18.9, 17.9, 26.2% reduction in blood sugar in alloxan-diabetic rabbits (150 mg/kg IV). Oral administration of 0.25 gm/kg allicin (isolated from *A. sativum*) produced hypoglycemia comparable to tolbutamide in mildly diabetic rabbits (glucose levels ranging from 180 to 300 mg %), while it showed no such effect in severely diabetic animals (blood sugar-/350 mg%). Aqueous homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 gm/kg/day in water for 2 months) significantly increased hepatic glycogen and free amino acid contents, decreased fasting blood sugar, triglyceride levels in serum, liver and aorta and protein levels in serum and liver in comparison to sucrose controls [17]. In subcutaneous glucose tolerance test in rabbits, garlic decreased hyperglycemic peak pretreatment with aged garlic extract (AGE) (5 and 10 ml/kg, p.o.) in stress induced hyperglycemia model of mice significantly prevented adrenal hypertrophy, hyperglycemia and elevation of cortisone without altering serum insulin levels. The efficacy of AGE was the same as that of diazepam (5 mg/kg, p.o.). Thus, AGE may prevent stress-induced risk of DM and its progression [18].

***Aloe barbadensis* (Asphodelaceae):** This plant has been widely cultivated throughout the world. Treatment of chronic but no single dose of exudates of *Aloe barbadensis* leaves shows hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also show hypoglycemic effect in diabetic rats. This action is through stimulation of synthesis and/or release of insulin from pancreatic beta cells [19] Chronic but not single administration of the exudate of the leaves of *Aloe barbadensis* (500 mg/kg p.o.) showed significant hypoglycemic effect in alloxan-diabetic mice. However, single as well as chronic administration of the bitter principle (5 mg/kg i.p.) showed significant hypoglycemic effect in the same model. The hypoglycemic effect of single dose of the bitter principle was extended over a period of 24 h with maximum hypoglycemia observed at 8 h while chronic administration (exudate twice daily and the bitter principle once a day for 4 days) showed maximum reduction in plasma glucose level at the 5th day.

***Aloe vera* (Asphodelaceae):** It grows in arid climates and is widely distributed in Africa, India and other arid areas. *Aloe vera* gel at 200 mg/kg had significant antidiabetic and cardioprotective activity and reduces the increased TBARS and maintains the Superoxide dismutase and Catalase activity up to the normal level and increases reduced glutathione by four times in diabetic rats [19]. The leaf pulp extract showed hypoglycemic activity on IDDM and NIDDM rats, the effectiveness being enhanced for type II diabetes in comparison with glibenclamide [20]. Both *Aloe vera* and *Aloe gibberellins* (over a dose range of 2-100 mg/kg) inhibit inflammation in a dose-response manner and improve wound healing in STZ diabetic mice. The dried sap of the plant (half a teaspoonful daily for 4-14 weeks) has shown significant hypoglycemic effect both clinically as well as experimentally [20].

***Anacardium occidentale* Linn. (Anacardiaceae):** It is originated from Brazil and is used in folk medicine in African countries, mainly in Cameroon for the treatment of diabetes mellitus. Hypoglycemic and protective role of *A. occidentale* was reported. The antihyperglycemic and renal protective activities of its leaves were reported in streptozotocin induced diabetic rats. It reduces diabetes-induced functional and histological alterations in the kidneys. It was shown that histopathological study of *A. occidentale* significantly reduced accumulation of mucopolysaccharides in the kidneys of diabetic animals [21].

***Annona squamosa* Linn. (Annonaceae):** It is commonly called custard apple in English and sharifa in Hindi. It is cultivated throughout India. The pharmacological active

ingredients are present in seeds, leaves and aerial parts of the plant. The study revealed that the plant possesses both hypoglycemic and antidiabetic activity. It acts by enhancing insulin level from the pancreatic islets, increases utilization of glucose in muscle and inhibits the glucose output from liver. Its margin of safety is high. The extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels [21].

Annona muricata **Linn. (Annonaceae):** It is commonly called soursop. It is small evergreen tree growing 5 to 6 meters in height. Young branches are rusty-hairy, the malodorous leaves and the plant is evergreen. *Annona muricata* is indigenous to most of the warmest tropical areas in South and North America, including the Amazon. The researchers revealed the immunohistochemical and biochemical effects of aqueous extract of leaves on pancreatic β-cells of STZ (streptozotocin) treated diabetic rats. *A. muricata* Linn. Leaf extract played important role in reduction of oxidative stress on pancreatic β-cells of streptozotocin treated diabetic rats. The treatment increased the area of insulin immunoreactive β-cells and partially prevents degeneration of β-cells [23].

Areca catechu **(Arecaceae):** It is a tall slender unbranched tree and is cultivated throughout India. Although, an epidemiological study has shown that nitrosmaines released during betel chewing may contribute to the risk of developing NIDDM, subcutaneous administration of alkaloid fraction of Areca catechu (0.05-0.5 mg/kg) in alloxanized rabbits (140 mg/kg) showed significant hypoglycemic effect lasting for 4-6 h [24].

Artemisia herba alba **(Asteraceae):** It is a perennial shrub that grows commonly on the steppes of Northern Africa, Arabian Peninsula, Western Asia and Southwestern Europe. Oral administration of 0.39 g/kg body weight of the aqueous extract of the leaves or barks produces a significant reduction in blood glucose level, while the aqueous extract of roots and methanolic extract of the aerial parts of the plant produce almost no reduction in blood glucose level. The extract of the aerial parts of the plant seems to have minimal adverse effect and high LD50 value [25].

Artemisia pallens: It is a shrub endemic to south India especially in Mysore state and is used in folk medicine as a treatment for DM in parts of south India. Oral administration of methanol extract of aerial parts of *Artemisia pallens* showed a dose-dependent (100, 500 and 1000 mg/kg) anti-hyperglycemic effect in glucose fed hyperglycemic and alloxanized rats (60 mg/kg IV). The effect was moderate in fasted normal rats but more in diabetic rats. Authors hypothesized that the plant extract increased peripheral glucose utilization or inhibited glucose reabsorption in the proximal tubules [26].

Astragalus membranaceus (Fisch.) **(Fabaceae):** It is used in traditional Chinese medicine. The protective mechanism of AGS-IV, a new glycoside of cycloartane-type triterpene isolated from the root of *A. membranaceus* (Fisch.) decreases the blood glucose concentration and HbAlC levels and increases plasma insulin levels. AGS-IV increases the activity of glutathione peroxidase in nerves, depress the activation of aldose reductase in erythrocytes and decreases the accumulation of advanced glycation end products in both nerves and erythrocytes. Moreover, elevates Na^+, K^+-ATPase activity in both the nerves and erythrocytes of diabetic rats. These results indicate that AGS-IV exerts protective effects against the progression of peripheral neuropathy in STZ-induced diabetes in rats through several interrelated mechanisms [27].

Averrhoa bilimbi **(Oxalidaceae):** This plant is mainly found in Asia and in some other parts of the world. At a dose of 125-mg/kg-body weight, the aqueous fraction (AF), butanol-soluble fraction (BuF) and the reference drug metformin (500 mg/kg body weight), produced significant blood glucose-lowering effect in the diabetic rats when compared to the vehicle (distilled water). Also Hepatic glucose-6-phosphatase activity in AF- and metformin-treated groups is lower, but not in BuF-treated groups, compared to that in vehicle-treated group. These results indicate that AF is more potent than BuF in the amelioration of hyperglycemia in STZ-diabeiic rats and is a potential source for the isolation of new orally active agent(s) for anti-diabetic therapy [28].

Azadirachta indica **(Meliaceae):** This is commonly known as Neem and is a tree native to India, Burma, Bangladesh, Sri Lanka, Malaysia and Pakistan and is growing in tropical and semi-tropical regions. A low (0.5g tid) and high (2g tid) doses of powdered part, aqueous extract and alcoholic extract of *Azadirachta indica* showed significant hypoglycemic activity in high dose and can be successfully combined with oral hypoglycemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents [29].

***Bauhinia candicans* (Leguminosae):** *Bauhinia candicans* is a medicinal plant indigenous to sub-tropical regions of Argentina and southern Brazil. The effect of different fractions of methanolic extract of *Bauhinia candicans* leaves (8 mg/kg) showed hypoglycemic activity along with a reduced urinary glucose excretion. Among the fractions, the butanolic fraction (B.U.F) exhibits highest activity. Moreover, B.U.F reduces plasma glucose level in normal, as well as, glucose loaded rabbits. These results suggest that *B. candicans* increases the peripheral metabolism of glucose [30].

***Bauhinia forficate* (Leguminosae):** *Bauhinia forficate* is the most widely used herbal medicine for control of diabetes in Brazil, where it is known as Pata de Vaca (cows hoof)(Ref…???). The fresh leaves are the essential part of this plant which shows the hypoglycemic activity and the genus *Bauhinia* belongs to the family Caesalpiniaceae. The initial reports of *Bauhinia forficata* antidiabetic activity in diabetic patients were made by Juliani [31] and Juliani [32]. According to Pepato *et al.,* [32] *Bauhinia forficate* decoction was prepared by boiling 150 g of fresh leaves in 1 litre of water for 5 min, allowed the decoction to stand for 30 min and filtered. The rats which are used for the experiment were fed a normal laboratory chow diet containing (*w/w)* 16% protein, 66% carbohydrate and 8% fat and were housed under a 12:12 h light: dark cycle at 22-25°C. In this experiment they divided the rats into two groups i.e., diabetic and non diabetic groups, followed by administered the streptozotocin (STZ) 40 mg/kg body weight, after 3 days the serum and urinary glucose levels were increased. Then one group was injected with *Bauhinia forficate* decoction and another with the drinking-water as control group. After 31 days of treatment the diabetic group treated with decoction showed a significant reduction in plasma glucose and urinary glucose. So the pharmacological, biochemical, histological and chemical studies are needed to elucidate the exact mechanism of action of *Bauhinia forficate* leaf decoction and to isolate any active compounds. Such investigations should also be carried out regarding type-2 diabetes [33].

***Biophytum sensitivum* (Oxalidaceae):** The annual perennial herbaceous plant is a traditional medicine in Nepal. Initial dose-response studies shows a dose of 200 mg/kg body weight is optimum for hypoglycemia. In 16-h fasted non-diabetic rabbits, a single administration brings about a 16.1% fall in fasting plasma glucose at the end of 1 and 2 h and the hypoglycemic effect persists at the end of 6 h (13.8% fall). Serum insulin levels shows a significant rise in the treated animals, which suggests a pancreatic mode of action (i.e. insulinotropic effect), suggesting that the hypoglycemic response of *B. sensitivum* may be mediated through stimulating the synthesis/release of insulin from the beta cells of Langerhans [34].

***Bixa orellana* (Bixaceae):** It is a shrub or small tree from the tropical region of the Americas and is known as annatto. This annatto extract decreases blood glucose levels in fasting normoglycaemic and streptozotocin-induced diabetic dogs. In normal dogs, it suppresses the postprandial rise in blood glucose after an oral glucose load and also causes an increase in insulin-to-glucose ratio in normal dogs. Increased insulin levels were not due to increased insulin synthesis, as after 1h residence time and half-hour postprandial, decreases C-peptide levels. It is concluded that *Bixa orellana* (annatto) lowers blood glucose by stimulating peripheral utilization of glucose and it is possible that this glucose-lowering extract might be of pharmacological importance [35].

***Boerhaavia diffusa* Linn. (Nyctaginaceae):** It is distributed widely all over India and is a small perennial creeping herb. The root and the whole plant are used as an Ayurvedic medicine in India and Unani medicine for the treatment of diabetes, stress, dyspepsia, abdominal pain, inflammation, jaundice, enlargement of spleen, congestive heart failure and bacterial infections. Aqueous leaf extract of the plant has been studied for its antidiabetic effect in alloxan-induced diabetic rats. The antidiabetic activity of the chloroform extract of the plant leaves on chronic treatment of streptozotocin-induced NIDDM (non insulin dependent diabetes mellitus) model diabetic rats was evaluated and the herb possesses antidiabetic activity. The herb mainly acts by reducing blood glucose level and increasing insulin sensitivity [36].

Bombax ceiba (family…..???): It is found throughout India especially in the forest region up-to an elevation of 1500 m. A C-flavonol glucoside isolated from *Bombax ceiba* leaves called as Shamimin has been shown to exert significant hypoglycemic activity at the dose of 500 mg/kg in rats [37]. The extract was lethal in rats at 500 mg/kg but not in mice even up to 1 gm/kg dose.

Brassica juncea(family…..???): It is commonly used spice in various food items in India. Oral feeding of Brassica juncea diet (10% w/w) for 60 days to normal rats led to significant hypoglycemic effect. This effect was

attributed to stimulation of glycogen synthetase (leading to increase in hepatic glycogen content) and suppression of glycogen phosphorylase and other gluconeogenic enzymes. Anti-oxidant and hypolipidemic activity is also described in literature [38].

***Brassica nigra* L (Brassicaceae):** It is an annual weedy plant cultivated for its seeds and is native to the southern Mediterranean region of Europe. Administration of 200 mg/kg body weight of aqueous extract to diabetic animals daily once for one month brings down fasting serum glucose (FSG) levels while in the untreated group FSG remains at a higher value. In the treated animals, the increase in glycosylated hemoglobin (HbAlc) and serum lipids is much less when compared with the levels in untreated diabetic controls [39].

***Bridelia ndellensis* Beille. (Euphorbiaceae):** A medicinal plant used in Cameroon against diabetes. The water and methanol extract of leaf of allied species *B. ferruginea* hav been proved as an active hypoglycemic agent in alloxan induced diabetic rats. The study of the glucose lowering of the ethanol extract and fractions of B. *ndellensis* stem bark in STZ (streptozotocin) type I and II diabetes rats at different prandial states was performed and significant lowering in blood glucose level was observed. The extract act by stimulation of islets cells and requires functional β-cells for its action [40].

***Bryonia alba* (Cucurbitaceae):** It is a flowering plant native to western Eurasia and adjacent regions, such as North Africa, the Canary Islands and South Asia. Administration of trihydroxyoctadecadienoic acids obtained from the roots of the native Armenian plant *Bryonia alba* L. (0.05 mg/kg/day for 15 days) restores the disordered lipid metabolism of alloxan-diabetic rats. Metabolic changes induced in diabetes significantly restores towards their normal values with the exception of diminished triglyceride content of muscle which does not restores. Thus, they can influence the profile of the formation of stable prostaglandins by actions downstream of prostaglandin endoperoxides [41].

***Bumelia sartorum* (Sapotaceae):** It has been mentioned in Brazilian folklore for its reputed use in the treatment of diabetes mellitus and inflammatory disorders. Bassic acid, an unsaturated triterpene acid isolated from ethanol extract *of Bumelia sartorum* root bark, elicits significant hypoglycemic activity and increases plasma insulin levels significantly in alloxan-diabetic rats and alters the pattern of glucose tolerance in these animals. Besides hypoglycemic activity, the extract also elicits significant anti inflammatory activity, but shows no significant effects on blood pressure, respiration or on the various isolated tissue preparations [42].

***Caesalpinia bonducella* (Fabaceae):** The oral administration of the extracts (300 mg/kg) produces significant antihyperglycemic action as well as lowers the BUN levels significantly. The action of the extracts on diabetes induced hyperlipidemia significantly lowers the elevated cholesterol as well as LDL level. The antihyperglycemic action of the extracts may be due to the blocking of glucose absorption. The drug has the potential to act as antidiabetic as well as antihyperlipidemic [43].

***Cajanus cajan* (Fabaceae):** Single doses of unroasted seeds (60% and 80%) on administration to normal as well as alloxanized mice shows significant reduction in the serum glucose levels after 1-2 hr and a significant rise at 3 hr. In case of roasted seeds, on other hand serum glucose levels increases during 3 hr experimental period. It is therefore concluded that roasting of seeds at high temperature for half an hour period results in the total loss of hypoglycemic principle but not the hyperglycemic principle present in the seeds [44].

Capparis decidua(family…..???): It is found throughout India especially in dry areas. Oral feeding of diet containing (30%) *Capparis decidua* fruit powder for 3 weeks to alloxanized (80 mg/kg IP) diabetic rats (blood glucose, 450 mg%) showed significant hypoglycemia (blood glucose, 120-130 mg%). In addition, anti-oxidant and hypolipidemic activity has been described in literature [45].

***Casearia esculenta* (Flacourtiaceae):** *Casearia esculenta* root (Roxb.) is widely used in traditional system of medicine to treat diabetes in India. Oral administration of aqueous extract of root (300 mg/kg body weight) for 45 days results in a significant reduction in blood glucose and in the activities of glucose-6-phosphatase and fructose-1, 6-bisphosphatase and an increase in the activity of liver hexokinase. However, in the case of 200 mg/kg body weight of extract, it shows less activity. The study clearly shows that the root extract of *C. esculenta* possesses potent antihyperglycemic activity but weaker than that of glibenclamide [46].

***Cassia auriculata* (Fabaceae):** *Cassia auriculata* occurs in the dry regions of India and Sri Lanka. Oral administration of CLEt- to mildly diabetic (MD) and severely diabetic (SD) rats at a dose of 400 mg/kg once a day for 15 days shows significant reduction in fasting blood glucose, also enhances the activity of hepatic hexokinase and phosphofructokinase and suppresses glucose-6-phosphatase and fructose-l,6-bisphosphatase in both MD and SD rats. Histopathological examination of pancreatic sections reveals increased number of islets and beta-cells in CLEt-treated MD as well as SD rats [47].

***Catharanthus roseus* Linn. (Apocyaceae):** It is commonly used as an anticancer agent, but the hot water decoction of the leaves and or the whole plant is used for the treatment of diabetes in subtropical and tropical areas of the world. The reports indicate blood glucose lowering activity in the alcoholic extract of the leaves of *C. roseus.* The herb have prophylactic activity against the necrotic actions of alloxan monohydrate. Antidiabetic activity of dichloromethane-methanol extract of the leaves and twigs was evaluated and its effect on enzymes of carbohydrate metabolism was studied. The mechanism may be due to enhanced secretion of insulin. The other researchers revealed that extract may be helpful in the prevention of damage caused by oxygen free radicals and increase in glucose utilization [48].

***Cocculus hirsutus* Linn. (Menispermaceae):** It's roots are bitter, acrid, laxative, demulcent and antiperiodic in fever, tonic and diuretic, also known as patalagarudi. The plant grows all over India, especially in dry regions. It is a straggling shrub, with softly villous young parts and resembles the plant path. Badole *et al*., [48] have demonstrated the antihyperglycemic activity of aqueous extract of leaves of *Cocculus hirsutus* (L) Diels in alloxan-induced diabetic mice. The antihyperglycemic potential of aqueous extract of *C. hirsutus* may be due to lowering serum glucose level in diabetic mice and increased glucose tolerance. Additionally, the extract prevents loss of body weight [49].

Citrullus colocynthis(family…..???): It is an annual herb found in wild as well as cultivated throughout India in the warm areas. The fruit of this plant is traditionally used as anti-diabetic in Mediterranean part of the World. Aqueous extract of its fruit showed dose-dependent increase in insulin release from isolated islets. Oral administration of aqueous extract (300 mg/kg) in normal rabbits significantly reduced plasma glucose after 1 h and highly significant reduction after 2, 3 and 6 h. Glycosidic extract (50 mg/kg) was more effective in lowering fasting glucose as compared to alkaloidal extract. Graded doses (10, 15 and 20 mg/kg) of saponin also reduced plasma glucose concentration in alloxanized rabbits. Thus, saponins and glycosidic components levels of the rind of *Citrullus colocynthis* are responsible for its hypoglycemic effect [50].

Coccinia indica(family…..???): It is a perennial tendril climber found throughout India. It is used in Ayurveda and Unani system of medicine for treatment of diabetes, skin eruptions, tongues sore, earache, etc. Feeding of water soluble alkaloid fraction of alcohol extract (1 gm/kg) of *Coccinia indica* leaves to normal fasting guinea pigs showed hypoglycemic activity of short duration and the effect was attributed to the presence of beta sitosterol. Oral administration (2 gm/kg/day) of pectin isolated from *C. indica* fruit showed a significant hypoglycemic action in normal rats due to stimulation of glycogen synthetase activity and reduction of phosphorylase activity.

Combretum micranthum(family.. ??): *Combretum Micranthum* is a medicinal plant used for treating diabetes in Northwestern Nigeria. It is commonly known as 'geza' in Hausa, belong to the family of Combretaceae. It is a widely known ethnomedicinal plant used in West Africa for treating several diseases. In Nigeria, more than 80% of the people depend on herbal medicines for treating their illnesses. The plant have also been documented to show antioxidant, antimicrobial as well as anti-inflammatory properties. The Aqueous extract of *Combretum micranthum* was prepared by using Soxhlet extractor and it was dried in an evaporator at 45ºC and stored at 4ºC until ready for use. The hypoglycemic activity of this plant extract was tested by using glucose tolerance test and fasting blood sugar assessment in normal rats. The antihyperglycemic potential of this plant was performed by taking two group of animals i.e., diabetic group and nondiabetic groups. The aqueous leaf extract of *Combretum micranthum* dissolved in normal saline (N/S) and administered to the both groups at 100 mg/kg, 200 mg/kg and 400 mg/kg body weight, but 100 mg/kg of the extract was found to be the optimum dose of the 3 doses. The aqueous leaves extract of 100 mg/kg body weight dose produced a significant reduction in blood glucose level and 24.6% maximum reduction when compared to the maximum decrease of 21.9% and 18.9% produced by 200 mg and 400 mg/kg body weight doses, respectively [51]. In this study, the aqueous leaves extract of *Combretum*

micranthum showed potential antidiabetic property for both type 1 and type 2 Diabetes mellitus. Hence further studies are needed to study the various active constituents responsible for these properties.

***Dioscorea dumetorum* Pax. (Dioscoreaceae):** It is used in treatment of diabetes in traditional medicine, possesses hypoglycemic effect. *D. dumetorum* Pax. Is commonly known as bitter yam. It occurs in Africa. An alkaloid present in an extract, dioscoretine, has been reported to possess hypoglycemic effect [41]. It has been reported that aqueous extract of *D. dumetorum* tuber control hyperlipidemia, hypercholesterolemia and hyperketonemia. The herb mainly act as an active hypoglycemic agent and works on the complications of diabetes [52].

***Elephantopus scaber* (Asteraceae):** *Elephantopus scaber* is an ethnomedicnal plant, having the property to reduce the blood glucose levels in streptozotocin induced diabetic rats significantly. It is popularly known as Elephant's foot, It is a scabrescent aromatic herb distributed in the moist deciduous forests of the central Western Ghats. The antidiabetic property of acetone extract was determined by taking control and streptozotocin induced diabetic rats. After 60 days of treatment with the acetone extract of *Elephantopus scaber* showed a significant decrease in blood glucose level from the initial 534.6 mg/dl to 86.14 mg/dl and reached a level closer to the untreated control of 85. 6 mg/dl. The antidiabetic property of plants shows their mechanisms by improving insulin sensitivity, augmenting glucosedependent insulin secretion and stimulating the regeneration of islets of langerhans in pancreas of STZ-induced diabetic rats. The administration of *Elephantopus scaber* acetone extract lowering the blood sugar level in streptozotocin induced hyperglycemic animals it may be due to a stimulating effect on insulin release from regenerated ß-cells of the pancreas or increased cellularity of the islet tissues and regeneration of the granules in the ß-cells [53].

***Eucalyptus globules* (Family….???):** It is a lofty tree of about 90 m in height and is grown in various part of India. Aqueous extract (0.5 gm/l) of eucalyptus increased peripheral glucose utilization in the mouse abdominal muscle and stepwise enhancement of insulin secretion from the clonal pancreatic beta cell line by 70-160%. Administration of Eucalyptus globulus leaves diet (6.25% w/w) for 12 days to normal rats did not result in hypoglycemia. In addition, STZ administration to these pre-treated rats did not produce hyperglycemia as severely as it was seen in controls. In addition, pre-treated rats also showed less polydypsia and body weight loss [54].

***Eugenia uniflora* (Family….???):** It is a large bushy shrub cultivated in garden. It is also distributed in southern Asia, Africa and in South America. Oral feeding of ethanol extract of the leaves of *Eugenia uniflora* to mice has been shown to contain plasma glucose levels during OGTT and plasma triglyceride level in oral corn oil tolerance test. Few fractions isolated on the basis of polarity and molecular size from the ethanolic extract of the leaves of *E. uniflora* has shown positive effects in OGTT conducted in mice. In addition all fractions except one showed dose-dependent inhibitory effect on lipase activity and these effects were apparently due to the inhibition of the decomposition of carbohydrates and fats in the intestine [55].

***Ficus bengalenesis* (Family….???):** A very large tree distributed throughout India from sea level to 1.200 m. A glucoside isolated from the bark of Ficus bengalenesis showed more potent hypoglycemic action as compared to crude ethanolic extract and the activity was half of tolbutamide. Oral administration of bark extract showed significant antihyperglycemic effect in STZ diabetic rats by raising serum insulin levels or inhibiting insulinase activity in liver and kidney. Oral administration of leucopelarogonidin derivative (100 mg/kg) isolated from bark of *F. bengalenesis* exerts significant hypoglycemic activity in normal and moderately alloxanized diabetic dogs (60 mg/kg IV injection). A leucocyanidin derivative (100 mg/kg) isolated from the bark of *F. bengalenesis* was hypoglycemic in normal rats. Combination of single dose of this chemical and low dose insulin controlled diabetes in alloxanized rats as effectively as that of high dose of insulin [56].

***Ficus hispida* Linn. (Moraceae):** It is also known as Daduri for the treatment of diabetes. This small tree may be found throughout India. Different workers have reported for the hypoglycemic effects of different compounds obtained from *F. bengalensis*. The hypoglycemic activity of *F. bengalensis* Linn. (bark) in normal and diabetic albino rats concluded that the water-soluble fraction of the alcoholic extract of *Ficus hispida* significantly decreases fasting blood glucose levels in normal and alloxan-induced diabetic rats.

The extract has direct peripheral action on β-cells but drug interaction can occur between *Ficus hispida* bark extract and insulin if given together [57].

***Garcinia kola* (Clusiaceae):** It is found in Africa mainly in subtropical or tropical moist lowland forests. The extract decreases the activity of microsomal glucose-6-phosphatase and lipid peroxidation (LPO) products. At a dose of 100 mg/kg, the fasting blood sugar in normoglycemic rabbits reduces from 115 mg/100 mL to 65 mg/100 mL after 4 h. In alloxan diabetic rabbits, the blood sugar lowers from 506 mg/100 mL to 285 mg/100 mL at 12 h. Kolaviron, a mixture of C-3/C-8 linked biflavonoids obtained from Garcinia kola produces significant hypoglycemic effects [58].

***Gymnema sylvestre* (Asclepiadaceae):** *G ymnema sylvestre* is emerging as a potential treatment for the management of diabetes, the leaves of this plant is used in herbal medicine preparations. *Gymnema* is a plant used in India and parts of Asia as a natural treatment for diabetes or "sweet urine." The hypoglycemic (blood sugar lowering) action of *Gymnema* leaves was first documented in the late 1920. The hypoglycemic effect was due to the ability of gymnemic acids to delay the glucose absorption in the blood. Because gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level and also the reduced glucose levels are exerted by the crude extract due to the presence of dihydroxy gymnemic triacetate had the ability to release the insulin by the stimulation of a regeneration process and revitalization of the remaining beta cells.

***Helicteres isora* (Sterculiaceae):** *Helicteres isora* distributed widely in forests throughout India. The hot water extract of fruit of *Helicteres isora* exhibits significant antioxidant activity and moderate antidiabetic activity at 200 mg/ml dose. It shows glucose uptake activity and found to be active comparable with insulin and metformin. The ethanolic extract has insulin-sensitizing and hypolipidemic activity and has the potential for use in the treatment of type-2 diabetes [59].

***Hibiscus rosa-sinesis* (Family….???):** *Hibiscus rosa-sinesis* is a shrub cultivated as an ornamental plant throughout India and has been mentioned in Ayurveda for its medicinal value. Single oral administration of 250-mg/kg ethanol extract of *Hibiscus rosa-sinesis* showed mild but significant hypoglycemia at 120 min in glucose loaded rat. Daily administration of the same dose for 7 days showed significant hypoglycemic effect at 30,90, 120 min after glucose loading in normal rats. The action was similar to tolbutamide and possibly due to insulin release by stimulation of pancreatic beta cells or an increase of the glycogen deposition in liver [60].

***Hypoxis hemerocallidea* Fisch. Mey. (Hypoxidaceae):** It is tuberous perennial plant which was previously known as *H. rooperi*. It is called wonder plant in South Africa and has been reported to be an effective remedy for the adult onset diabetes mellitus. The methanolic extract of *H. hemerocallidea* was reported for its hypoglycemic effect in normoglycemic and in streptozotocin-induced diabetic rats, the herb can be used as hypoglycemic agent and it has property to cure the adult onset diabetes mellitus. The action of the herbal plant material is not yet clear [61].

***Inula racemosa* (Asteraceae):** It grows in the temperate and alpine western Himalayas. The petroleum ether extract of roots lowers plasma insulin and glucose levels within 75 min of oral administration to albino rats and it significantly counteracts adrenaline-induced hyperglycemia in rats. The extract further shows negative inotropic and negative chronotropic effects on frog heart. All these findings indicate that one of the constituents of *Inula racemosa* may have adrenergic beta-blocking activity [62].

Ipomoea batatas (Family..??): A trailing herb cultivated for its succulent tuberous roots. Oral administration of *Ipomoea batatas* reduces hyperinsulinemia in Zucker fatty rats by 23, 26, 60 and 50% after 3, 4, 6 and 8 weeks, respectively. In addition, inhibition of blood glucose level after glucose loading was observed after 7 weeks of treatment along with regranulation of pancreatic beta cells and reduction in insulin resistance. Hypolipidemic activity has also been described [63].

Lantana camara (Family..??): A large aromatic shrub found throughout India. It is mentioned in Ayurveda for treatment of various vitiated body conditions. Once daily administration of *Lantana camara* leaves juice (1500 mg/kg/day for 14 days) showed significant hypoglycemic effect in rats. However, the plant is hepatotoxic in nature [64].

***Lepidium sativum L* (Brassicaceae):** It is a fast-growing, edible herb. The aqueous *Lepidium sativum* extract at a dose of 10 mg/kg/h causes a potent inhibition of renal glucose reabsorption which in turn reduces blood sugar. This renal effect is at least one mechanism explaining the hypoglycemic activity of this plant in normal and diabetic rats [65].

***Liriope spicata* (Liliaceae):** *Liriope spicata* is a Chinese medicinal plant, which belongs to Liliaceae family. It is frequently used as "maidong" in prescriptions of traditional Chinese medicine for the treatment of Diabetes mellitus, because of the high availability and safety. The antidiabetic effect it is due to presence of two important main active components in water extracts as well as crude polysaccharides [66]. The aqueous extract was administered at dose of 100mg/kg and 200gm/kg to two groups i.e., control and diabetic rats, after 28 days of treatment it shows significant decrease in the blood glucose level in streptozotocin induced diabetic rats.

***Mangifera indica* (Family…..??):** The tree is found throughout India and traditionally its seeds and fruits are used for treatment of various ailments. Oral administration of aqueous extract of the leaves (1 gm/kg) failed to alter the blood glucose levels in normoglycemic or STZ induced diabetic rats. However, the extract showed anti-diabetic activity when given 60 min before or concurrently with glucose and this action could be due to reduction in intestinal absorption of glucose. However, possibility of other mechanism can not be excluded. *Mangifera indica* has also been shown to exert powerful anti-oxidant activity *in vitro* [67].

***Momordica charantia* (Cucurbitaceae):** *M. charantia* (bitter melon) is commonly known as vegetable insulin. An oral sucrose tolerance test reveals that administration of aqueous extract (AE), methanol fraction (MF) or methanol insoluble fraction (MIF) each significantly suppresses plasma glucose levels at 30 min as compared with control. In addition, the plasma insulin level at 30 min also lowers after MF administration than the control in the oral sucrose tolerance test, these results demonstrates that bitter melon suppresses postprandial hyperglycemia by inhibition of á-glucosidase activity [68].

***Morinda lucida* (Rubiaceae):** The extract of *Morinda lucida* demonstrates a significant and dosedependent hypoglycemic activity within 4 h after oral administration in normal rats. In hyperglycemic rats, the extract produces a significant anti-diabetic effect from day 3 after oral administration, with 400 mg/kg extract-treated animals. These results suggest that the leaves of *Morinda lucida* have a strong glucose lowering property when administered to streptozotocin-treated rats [69].

***Murraya koenigii* Linn. (Rutaceae):** It is commonly known as Curry patta and is widely used condiment and spice in India. In normal and alloxan diabetes the aqueous extract of the leaves of *M. koenigii* produced hypoglycemic effect. Oral feeding of this plant for 60 days diet to normal rats showed an increase in the concentration of hepatic glycogen due to hypoglycemic activity. It has been reported that feeding different doses of *M. koenigii* leaves to diabetic rats play a role in control of mild diabetic rats to moderate, severe and type I diabetes [70].

***Ocimum sanctum* (Lamiaceae):** It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves shows significant reduction in blood sugar level in both normal and alloxan induced diabetic rats. Significant reduction in fasting blood glucose, uronic acid, total amino acids, total cholesterol, triglyceride and total lipid indicate the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats. Oral administration of plant extract (200 mg/kg) for 30 days leads to decrease in the plasma glucose level. Renal glycogen content increases 10 fold while skeletal muscle and hepatic glycogen levels decreases by 68 and 75% respectively in diabetic rats as compared to control [71]. This plant also shows antioxidant, antibacterial, antifungal, antiviral, antiasthemitic, antistress, antitumor, gastric antiulcer activity, antimutagenic and immunostimulant activities (Ref..??).

***Panax ginseng* (Araliaceae):** The roots of *Panax ginseng* are taken orally in the treatment of type II diabetes. Extracts of ginseng species shows antihyperglycemic activity associated with increased peroxisome proliferator-activated receptor gamma expression and adenosine monophosphate-activated protein kinase phosphorylation in liver and muscle. Oral administration of *Panax ginseng* root improves insulin sensitivity and may be used as an adjuvant therapy for treating diabetic patients with insulin resistance [72].

Picrorrhiza kurroa(family…??): It is small herb found in the Himalayan region from Kashmir to Sikkim. Alcoholic extract of Picrorrhiza kurroa (75 mg extract/kg) reduced serum glucose that was maximum 2 h after the dose. It also showed antihyperglycemic effect in alloxanized diabetic rats. Serum glucose decreased by 43 and 60% with 75 and 150 mg/kg of the extracts, respectively [73].

***Punica granatum* (family…??):** A shrub or small tree grows wild in the warm valleys and outer hills of the Himalayas and also cultivated throughout India. The flowers of *Punica granatum* are used as anti-diabetic in Unani medicine called Gulnar farsi. Oral administration of aqueous-ethanolic extract (50% v/v) led to significant blood glucose lowering effect in glucose fed hyperglycemic and alloxanized diabetic rats with the maximum effect at the dose of 400-mg/kg body weight. Anti-oxidant activity has been described in the literature [74]. Swertia chirayita: Chirata (Hindi) It is mainly found in temperate Himalayas between the height of 1200 and 1300 m. Various crude extracts and its isolated fractions have shown hypoglycemic activity in various animal models. Oral administration of ethanolic extracts (95%) and hexane fraction of *Swertia chirayita* (10, 50 and 100 mg/kg) to normal, glucose fed and STZ induced diabetic rats significantly lowered blood glucose in all groups of animals. Out of 95% ethanol extract and its four fractions (each 250 mg/ kg) tested in fasted, fed, glucose-loaded and tolbutamide-pretreated animal models, hexane fraction caused a maximum lowering of blood sugar in all but fasted rats [75].

***Terminalia chebula* Retz. (Combretaceae):** It 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 [76].

***Tinospora cordifolia* (Menispermaceae):** Commonly known as Guduchi, an herbaceous vine indigenous to the tropical areas of India, Myanmar and Sri Lanka. Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats causes a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant antihyperglycemic effect in different animal models, its effect is equivalent to only one unit/kg of insulin [77].

***Trigonella foenum graecum* (Fabaceae):** *Trigonella foenum graecum* used as herb (the leaves) and as a spice (the seed) and cultivated worldwide as a semi-arid crop. Oral administration of 2 and 8 g/kg of plant extract produces dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats. Administration of fenugreek seeds improves glucose metabolism and normalizes creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduces hepatic and renal glucose-6-phosphalase and fructose -1, 6-biphosphatase activity [16].

CONCLUSION

Currently, many countries face large increases in the number of people suffering from diabetes. The World Health Organization 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 [78]. In spite of the presence of known antidiabetic medicine in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease. Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones. Based on the WHO recommendations, hypoglycemic agents of plant origin used in traditional medicine are important. The attributed antihyperglycemic effects of these plants are due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or a decrease in the intestinal absorption of glucose. Hence, treatment with herbal drugs has an effect on protecting β-cells and smoothing out fluctuation in glucose levels. In general, there is very little biological knowledge on the specific modes of action in the treatment of diabetes, but most of the plants have been found to contain substances like glycosides, alkaloids, terpenoids, flavonoids etc. that are frequently implicated as having antidiabetic effects. The research for alternate remedies (from the plant kingdom) for diabetes mellitus will continue all over the world as the disease poses many challenges not only to the physician but also to the researcher.

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