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MEDICINAL PLANTS: CURRENT ADVANCEMENT AND APPROACH IN THE THERAPY OF DIABETES MELLITUS

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Abstract
India is rich in traditional plant based knowledge on healthcare. A large number of medicinal plants/plant extracts/decoctions or pastes are equally used by tribals as folklore in India for the treatment of diabetes. The review presents comprehensive details on some of the recent activities performed in traditionally claimed antidiabetic activity from various parts of the world. The bioactive extracts along with potent phytoconstituents and compounds isolated from such plants have been summarized and pharmacological studies performed on the experimentally induced diabetic animals. It is proposed that this review will help the researchers to undertake further research regarding these plants and in isolation of active compounds with antihyperglycemic property to develop potent and novel antidiabetic compounds in future.

Key words
Medicinal plant,
Folklore,
Antidiabetic,
Phytoconstituents.

INTRODUCTION

Diabetes mellitus (DM) consists of a group of symptoms characterized by hyperglycemia, increased metabolism of lipids, carbohydrates and protein and an increased risk of complications from various diseases [1]. In simplest term, diabetes mellitus results when pancreatic beta cells are unable to maintain adequate insulin secretion or the cells of the body does not responding properly to the insulin produced. Diabetes mellitus is a chronic metabolic disorder affecting a large portion of the population worldwide [2] and it has an increasing prevalence due to several factors, such as urbanization, sedentary lifestyle, obesity, food habits, stress etc[3]. It is estimated that diabetes affects at least 366 million people worldwide, and the number is expected to reach 552 million by the year 2030, with two third of all diabetes cases occurring in low to middle income countries. The number of adults with impaired glucose tolerance will rise from 280 million in 2011 to an estimated 298 million by 2030 [4].

The vast majority of cases of diabetes fall into two broad etiopathogenic categories as type 1 diabetes where the cause is deficiency of insulin secretion associated with auto-immune destruction of insulin producing pancreatic β-cells, and is hereditary [5]. It often occurs in children and young adults. In Type 2 diabetes, which accounts for more than 90% of cases, is caused by a combination of resistance to insulin action and impaired insulin secretion [6]. The chronic hyperglycemia of diabetes is associated with profound alterations in the plasma lipid and lipoprotein profile and therefore is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [7].

Insulin is the drug of choice in controlling hyperglycemic state in Type 1 and sometimes for Type 2 diabetes. The classes of drugs widely used in the treatment of type 2 diabetes are metformin, glibenclamide, rosiglitazone, acarbose, vildagliptine etc., which are used as monotherapy or in combination.

Various chemicals have been used to induce experimental diabetes in rodents, particularly streptozotocin (STZ), which has been extensively used in diabetes research. The development of hyperglycemia, following STZ injection is primarily due to the direct pancreatic β-cell destruction resulting insulin deficiency in dose dependent manner [8,9].

Despite the great interest in the development of new drugs to prevent the burden of complications associated with this disease and the raised interest in the scientific community to evaluate either raw or isolated natural products in experimental studies, only a few of them made into the clinical setting [10-13]. Many synthetic hypoglycemic agents are currently available but, they produce undesirable side effects on chronic use or are either too expensive [14].

Plants have always been an exemplary source of drugs and many of the currently available drugs have been derived directly or indirectly from them. A number of indigenous plants have been widely used for the treatment of diabetes and several other ailments [15,16]. The ethno botanical information reports about 800 plants that may possess anti diabetic potential [17]. Few of the traditional plant treatments for diabetes have received scientific scrutiny, and the World Health Organization [18] has recommended that this area warrants attention. The effects of these plants may delay the development of diabetic complications and even assist in correcting the metabolic abnormalities. Moreover, during the past decade and especially in the last few years some of the new proactive compounds isolated from hypoglycemic plants showed antidiabetic activity with more efficacy than synthetic oral hypoglycemic agents [19,20]. However, a number of plants with such potentials remain unexplored. The aim of presenting this review article is to furnish a brief and updated data related to some recently studied anti-diabetic plants worldwide. Literature survey was performed via electronic search (Pubmed®, SciFinder® and Google Scholar) on papers published in English from 2010 to 2015, using terms natural products, hypoglycemic and diabetes mellitus treatment. Some of the important antidiabetic potential herbal plant source and its possible mechanism of action are summarized in table 1.

IMPORTANT MEDICINAL PLANTS HAVING ANTIDIABETIC ACTIVITY

***Acorus calamus* [21]**

The antihyperglycemic activity of methanolic extract of *A. calamus* rhizome at a dose of 200 mg/kg in streptozotocin (STZ) induced diabetic rats was investigated. The extract caused reduction in the activity of liver enzymes in plasma such as AST, ALT, ALP of diabetes treated group and consequently alleviated liver damage caused by STZ induced diabetes. There was significant reduction in blood glucose, lipid profile, glucose 6-phosphatase, fructose 1,6 bis phosphatase levels and hepatic markers enzymes when compared to diabetic control. The phytotreatment showed more efficient antihyperglycemic activity than the standard drug glibenclamide.

***Albizzia lebbeck* [22]**

The methanol/dichloromethane extract (100, 200, 300, 400 mg/kg body weight) of the powdered stem bark of *A. Lebbeck* was evaluated for its antihyperglycemic activity in Streptozotocin induced diabetic rats. The extract (400 mg/kg body weight) and Glibenclamide (1 mg/kg body weight) reduced the blood glucose level to a significant level ($p < 0.05$) after 2 h of oral administration as compared to the diabetic control. The extract ameliorates the hypoglycemia mediated oxidative stress as well as corrects the lipid profile, hepatic and renal parameters, which was evidenced by improved glycemic control, lipid, renal, hepatic as well as antioxidant biochemical parameters.

***Andrographis paniculata* [23]**

The antidiabetic activity of the aerial part of *A. paniculata* powder (500 mg/kg body weight) was evaluated in high fat and sucrose induced type-2 diabetic adult male rat. Treatment to diabetic group was able to significantly lower the blood glucose level similarly to the metformin treated (50 mg/kg body weight) diabetic group. The antihyperglycemic effect of *A. paniculata* may be attributed to several mechanisms such as its ability to a) increase glucose uptake and oxidation in the peripheral tissues; b) impair absorption of glucose at the intestine (α-glucosidase inhibition) ; c) enhance insulin sensitivity and thereby increasing the glucose transporters; d) control lipid metabolism thereby mending the putative inhibition of insulin signaling; e) scavenge the free radicals (antioxidant activity) which disrupt the plasma membrane integrity, resulting in

decreased plasma membrane receptors necessary to signal and uptake glucose from the blood stream.

***Areca catechu* [24]**

Anti diabetic activity of petroleum ether, chloroform and methanol extracts of *A. catechu* leaf were evaluated in streptozotocin induced diabetic rats. All the extracts at 200 mg/kg orally significantly ($p < 0.001$) exhibited anti diabetic activity by reducing and normalizing the elevated fasting blood glucose levels as compared to those of streptozotocin treated group. The methanol extract was most active followed by chloroform and pet. ether extracts respectively. The test extracts decreased the elevated serum enzyme activities, cholesterol contents with elevation of total protein content in the STZ treated rats which are comparable to the normal control group. The observed antidiabetic activity of all the extracts may be mainly due to the presence of triterpenoid compounds.

***Aristolochia indica* [25]**

The active component Stigmast-5-en-3β-ol (β-sitosterol) was isolated from the chloroform extract of aerial part of *A. indica* and its antihyperglycemic activity was evaluated in alloxan-induced diabetic mice. There was decrease in the serum glucose level in diabetic mice. The compound also exhibited antioxidant activity estimated through the scavenging of free radicals such as DPPH and superoxide radical. The compound seems to be rich source of natural antioxidants which can be accounted for the traditional uses in prevention of diabetes and conservation of good health. The anti-hyperglycemic effect of the extract was seen at different doses of 100, 250, 500 and 750 mg/kg body weight in increasing order which may be attributed to an increase in peripheral glucose consumption as well as protection against oxidative damage in alloxanised diabetes.

***Artemisia afra* [26]**

Aqueous leaf extract of *A. afra* at doses of 50, 100, and 200 mg/kg body weight in streptozotocin induced diabetic rats showed significantly ($P < 0.05$) increased body weight, decreased blood glucose levels, increased glucose tolerance, and improved imbalance in lipid metabolism in diabetic rats. The activity of the extract at a dose of 200 mg/kg body weight is comparable with glibenclamide, a standard hypoglycemic drug. The extract at all dosages tested also restored liver function indices and haematological parameters to normal control levels in the diabetic rats. This investigation clearly showed that in addition to its hypoglycemic activity, *A. afra* may also protect the liver and blood against impairment due to diabetes.

***Barleria prionitis* [27]**

The antidiabetic activity has been performed in the alcoholic leaf extract of *B. prionitis* against alloxan induced diabetic rats. It was found that administration of leaves extract at dose 200 mg/kg body weight shows 130% and 96.68% significant increase in serum insulin and liver glycogen respectively. The mechanism of the extract is similar to Biguanides which may be attributed to the presence of flavonoids.

***Buchholzia coriacea* [28]**

The study demonstrated the hypoglycemic activity and ameliorative effects on Streptozotocin (STZ) induced diabetic mice and rats. It is found that the ethanolic and butanolic seed extract of *B. coriacea* significantly decreases blood glucose on STZ-induced diabetic rats. Presence of flavone glycoside that possess the antioxidant and hypoglycemic potential helped in alleviating the complications associated with diabetes.

***Caesalpinia digyna* [29]**

The bergenin has been isolated from the ethanolic dried root extract of *C. digyna* which demonstrated antidiabetic property. Bergenin at different doses 2.5, 5 & 10 mg/kg body weight shows prominent decrease in blood glucose level on STZ-nicotinamide induced diabetic rats. It is thought that the antidiabetic effect of bergenin may be due to positive influence on endocrine cells of the pancreas resulting in increased production of insulin. It also possesses the antioxidant properties with the protective effect on rat pancreas, due to regeneration of intact β-cells.

***Capparis tomentosa* [30]**

Antidiabetic activity of the aqueous root extracts of *C. tomentosa* were investigated in alloxanised mice. Extracts at a dose of 50, 100 and 200 mg/kg body weight were given orally. Extract exhibited dose dependent hypoglycemic activity that is significantly higher than that of the reference drug glibenclamide. Extract at a dose of 200 mg/kg body weight reduced blood glucose level from 28.4 mmol/l to 4.7m mol/l whereas glibenclamide at a dose of 3mg/kg body weight decreased glucose level to 4.9mmol/l.

***Carissa carandas* [31]**

It has been revealed that the methanolic extract of fruits of *C. caradas* and its ethyl acetate soluble fraction (CCES) significantly lowered blood glucose in alloxan monohydrate induced rats. It is thought that increased antihyperglycemic activity of CCES fraction (64.5%) at dose level of 400 mg/kg body weight may be due to the higher degree of polymerization which is also responsible for increased cytotoxic, anti-inflammatory and immunomodulatory activity increase. Other

secondary metabolites such as steroids and polyphenolics present in CCES fraction might play important role in its antidiabetic potential.

***Catathelasma ventricosum* [32]**

Selenium-polysaccharide obtained from *C. ventricosum* was purified by DEAE-52 and Sephadex G-100 column chromatography. The antidiabetic potential of polysaccharide was tested in streptozotocin induced diabetic mice. After STZ induced diabetic mice being administered polysaccharide for 30 days, the treatment significantly reduced the levels of malondialdehyde (MDA) and low-density lipoprotein cholesterol (LDL-C) that were increased by the STZ treatment. Further, the polysaccharide treatment led to increased activity of antioxidant enzymes in liver and kidney and high density lipoprotein cholesterol (HDL-C) that were decreased by the STZ. The results of histopathology also showed polysaccharide protected tissues (pancreas, liver and kidney) against peroxidation damage and maintained tissue integrity. The level of hepatic glycogen and insulin in Glibenclamide treated mice was almost normalized. Compared with glibenclamide, the antihyperglycemic action of polysaccharide is ascribed partially to insulin secretion and subsequent glycogen synthesis.

***Cestrum nocturnum* [33]**

Hydroalcoholic extract of *C. nocturnum* leaves showed significant ($P < 0.01$) antidiabetic activity at both doses i.e. 200 and 400 mg/kg of body weight on streptozotocin-induced diabetic rats. The extracts given once a day for 15 days showed significant reduction in blood glucose level which is comparable to the standard metformin at a dose of 10mg/kg. The body weight of the animals also increased and there was improvement in the biochemical parameters associated with diabetes. Increase in body weight and decrease in blood glucose might be due to improvement in the glycemic control mechanisms and insulin secretions from remnant pancreatic cells in diabetic animals.

***Citrus limetta* [34]**

The antihyperglycemic effect of *C. limetta* fruit peel has been evaluated on STZ-induced diabetic rats. The study has shown that oral administration of methanolic extract of *C. limetta* at dose 200 and 400 mg/kg body weight significantly decreases the increased blood glucose level in rats. The antidiabetic effect may be due to antioxidant property of the extract.

***Cocus nucifera* [35]**

The study has been performed to investigate the antihyperglycemic activity of hydro-ethanolic extract of *C. nucifera* on STZ induced diabetic rats. It has been revealed that oral administration of this extract at dose 500 mg/kg body weight significantly reduces the increased blood glucose in comparison to glibenclamide (0.5 mg/kg). The antidiabetogenic potential of the plant extract is attributable to increase in insulin from existing β-cells or its release from the bound insulin.

***Dracaena cochinchinensis* [36]**

Antidiabetic activity of the total flavonoids obtained from *D. cochinchinensis* was evaluated in type 2 diabetes mellitus rats. Type 2 diabetes in rats were induced by 4 weeks high fat diet and a singular injection of streptozotocin (STZ) (35 mg/kg). Flavonoids (77.36%) administrated via oral gavage not only exhibited a significant hypoglycemic activity, but also alleviated dyslipidemia, tissue steatosis, and oxidative stress associated with T2DM. the hypolipidermic activity of flavonoids is similar to that of the standard drug metformin (200 mg/kg).

***Ducrosia anethifolia* [37]**

Antidiabetic activity of the ethanolic crude extract (500 mg/kg body weight) and major isolated furanocoumarins from *D. anethifolia* were evaluated in streptozotocin induced diabetic rats. In STZ group, a significant increase was observed in blood glucose level with percentage increase reaching 227.26% which was decreased to 178.78% on treatment with the extract and to 191.42% with glibenclamide. There was also significant reduction in total cholesterol (TC) and triglycerides (TGs) after the treatment with D. enthifolia extract as compared to glibenclamide treated group.

***Durio zibethinus* [38]**

The ethanolic extract of *D. zibethinus* fruit peels with each dose of 125, 250, and 500 mg/kg body weight were evaluated for antidiabetic effects on alloxan induced diabetic rats. The ethanolic extract of *D. zibethinus* at a dose of 500 mg/kg body weight reduced blood glucose level by 50.19% whereas glibenclamide at a dose of 0.45 mg/kg body weight decreased blood glucose level by 41.95% only as compared to control. The ability of ethanolic extract in reducing blood glucose levels is presumably because of flavonoids constituents.

***Entada phaseoloides* [39]**

It has been revealed that total saponins from *E. phaseoloides* (TSEP) showed effective antidiabetic activity in type 2 diabetic rats which was induced by high-fat diet and low-dose STZ. It has shown that oral administration of the compound at dose of 25, 50 and 100 mg/kg body weight reduces fasting blood glucose and increase serum insulin levels in a dose dependant manner. It is thought that the hypoglycemic activity is by improvement in peripheral insulin resistance. It also

showed hypolipidemic acitivity and an improvement in tissue steatosis more as compared to metformin. The anti-inflammatory effect of TSEP has also been suggested due to decrease in the serum levels of interleukin-6 (IL- 6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP).

***Eugenia singampattiana* [40]**

The ethanolic extract of leaves of *E. singampattiana* was investigated for its antioxidant, antihyperlipidaemic and antidiabetic effect in alloxan induced diabetic rats. The extract at a dose of 150 and 300 mg/kg of body weight showed significant reductions of blood glucose ($P<0.05$), lipid parameters except HDL-C, serum enzymes and significantly increased HDL-C and antioxidant enzymes. The extracts also caused significant increase in plasma insulin ($P<0.05$) in the diabetic rats. The possible antidiabetic activity of the extracts might be due to stimulation of residual pancreatic insulin or by increasing peripheral utilization of glucose. Flavonoids and phenols which are the active phytochemicals present in the extract are reported to regenerate the damaged pancreatic beta cells and have been found to be effective antihyperglycemic agents.

Gymnema montanum (41)

The antidiabetogenic activity has been demonstrated in alcoholic stem extract of *G. montanum*. The extract at 100 and 200 mg/kg body weight dose has been found to decrease the increased glucose level on STZ induced diabetic rats. The activity may be due to increased pancreatic secretion of insulin from existing β cells.

***Gynura procumbens* [42]**

Serial ethanolic extracts of *G. procumbens* leaves extracted sequentially with graded percentage of ethanol in water (95%, 75%, 50%, 25% and 0%) were tested for antidiabetic activity in streptozotocin induced diabetic rats. The 25% extract exerted prompt reduction in fasting blood glucose level and sustained reduction till end of the study comparable to the effect of metformin . In the study it was seen that the extract contains active principles that possess antihyperglycemic but no hypoglycemic activity effect. This activity is most potent when extracted in 25% ethanol- water solvent combination. The extract may achieve its antidiabetic action via a mechanism similar to metformin.

***Gynura procumbens* [43]**

The antidiabetic activity of aqueous and ethanolic extract of *G. Procumbens* leaves have been performed. The study revealed that both extracts at doses of 50, 100 and 150 mg/kg body weight showed the lowering of blood glucose level in a dose dependent manner on STZ induced diabetic rats. It has been found that ethanolic extract showed better reduction of blood glucose and HbA1c levels than aqueous extract. The antidiabetic potential may be attributable to increase in glucose metabolism via the glycolytic pathway and inhibition of hepatic endogenous glucose production via the gluconeogenic pathway.

***Impatiens niamniamensis* [44]**

Hypaphorine have been isolated from the ethanolic dried seed extract of *I. niamniamensis*. The study has revealed that the ethanolic extract and isolated hypaphorine at dose 200 mg/kg and 50 mg/kg respectively possess hypoglycemic activity against STZ induced diabetic rats.

***Juniperus oxycedrus* [45]**

Shikimic acid has been isolated from the ethanolic dried berries extract of *J. oxycedrus.* Shikimic acid at dose of 15 and 30 mg/kg body weight revealed the antihyperglycemic activity on STZ-induced diabetic rats. It is also found to reduce malondialdehyde (MDA) levels on kidney and heart tissues significantly (64.5–63.2%). The antidiabetic activity may be due to the increased mRNA expression of insulin like growth factor-1 (IGF-1).

***Kalanchoe pinnata* [46]**

Dichloromethane (DCM) fraction of *K. pinnata* leaves at a dose of 5 and 10 mg/kg body weight was tested for antidiabetic activity in streptozotocin-induced diabetic rats. Fasting blood glucose values were reduced to 116 mg/dl from 228 mg/dl on treatment with 10 mg/kg body weight of DCM fraction, while glycated hemoglobin improved to 8.4% compared with 12.9% in diabetic controls. The insulin level and lipid profile values were close to normal values. In vitro studies demonstrated a dose-dependent insulin secretagogue action. Insulin secretion was 3.29 fold higher at 10 mg/ml as compared to the positive control. The insulin secretagogue activity was glucose independent and K+ ATP channel dependent. The bioactive component of the DCM fraction was identified to be a phenyl alkyl ether derivative.

***Lageneria siceraria* [47]**

The study has been performed to evaluate the hypoglycemic potential of *L. siceraria*. It has been found that oral administration of methanolic extract of *L. siceraria* at dose of 200 and 400 mg/kg body weight reduces the blood glucose significantly on STZ-induced diabetic rats. It is also found to possess antioxidant potential. It has also revealed the presenece of high phenolic and flavonoid contents and the results are expressed as 65.7±0.46 mg/g pyerocatechol equivalent and 25.3±0.86 mg/g quercetin equivalent respectively.

The mechanism of action is attributable to high flavonoid and phenolic content of the extract.

***Leonotis leonurus* [48]**

The antidiabetogenic potential of aqueous leaf extract of *L. Learners* have been investigated against STZ-induced diabetic rats. It has been found that oral administration of extract at doses of 125, 250 and 500 mg/kg body weight reduces increased blood glucose level significantly. It has also shown to possess high phenolic and flavonoid contents and the results are expressed as 48 mg/g tannic acid equivalent and 4.8 mg/g quercetin equivalent respectively. The antidiabetic activity is attributable to high flavonoid and phenolic content of the extract.

***Marrubium vulgare* [49]**

The antihyperglycemic activity of aerial parts of *M. vulgare* has been demonstrated in alloxanized diabetic rats. Oral administration of the aqueous extract at doses of 100, 200 and 300 mg/kg body weight has showed the lowering of blood glucose level in a dose dependent manner in alloxanized diabetic rats. The antidiabetic potential may be attributable to inhibition of insulin degradation or stimulation of insulin secretion in the presence of flavonoids and acteoside.

***Merremia emarginata* [50]**

Methanolic extract of *M. emarginata* at different doses of (100, 200 and 400 mg/kg) possess antihyperglycemic effect in streptozotocin induced model of rats. The antihyperglycemic activity of the extract was associated with an increase in plasma insulin levels, suggesting an insulinogenic activity of the plant extracts. There was significant decrease in blood glucose, serum urea and serum creatinine level. Histology of diabetic rats treated with Merremia emarginata showed the pancreatic cell regeneration.

***Merremia tridentate* [51]**

Antidiabetic effect of aqueous root extract of *M. tridentate* at different doses of 50, 100 and 150 mg/kg body weight was evaluated in normal, glucose-loaded hyperglycemic and streptozotocin (STZ) induced diabetic rats. The extract reduced elevated blood glucose level and lipid profile of STZ induced diabetic rats, but has no effect on normal rats. Attenuation of increased lipid peroxidation could be due to the antioxidant effect of flavonoids present in the extract. The possible mechanism by which the extract mediated its antidiabetic effect could be by potentiation of pancreatic secretion of insulin from existing β cells of islets.

***Momordica charantia* [52]**

The antidiabetic potential of ethanolic leaf and seed extract of *M. charatia* has been evaluated. The study included the isolation of saponin rich fractions and 5 isolated compounds namely 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al, momordicine I, momordicine II, 3-hydroxycucurbita-5,24-dien-19-al-7,23-di-O-β glucopyranoside and kuguaglycoside G. The insulin secreting activity has been evaluated using MIN6 β-cells. The hypoglycemic activity may be due to increased insulin secretion.

***Moringa oleifera* [53]**

The antidiabetic activity of two low doses of *Moringa oleifera* seed powder (50 and 100 mg/kg body weight, in the diet) on streptozotocin (STZ) induced diabetic male rats was investigated. The concurrent treatment with Moringa ameliorated various problems caused by using streptozotocin in rats such as increase in serum glucose and increase in glycosylated hemoglobin, increase in lipid peroxidation and IL-6 and decreased catalase, SOD, and GSH activity in the serum and the kidney tissue homogenate compared with that of the negative control group. This curative effect is due to the the antioxidant activity of Moringa seed powder which is due to its content of phenolics and flavonoids that have scavenging effect on the free radicals.

***Passiflora incarnate* [54]**

The hypoglycemic and hypolipidemic effects of methanolic extract of leaves of *P. incarnate* at doses of (100 and 200 mg/kg) for 15 days has been seen in streptozotocin-induced diabetic mice. The extracts showed improvement in parameters like oral glucose tolerance, body weight, urine glucose, liver glycogen and lipid profile as well as regeneration of pancreatic islets of Langerhans and so might be valuable in diabetes treatment.

***Picralima nitida* [55]**

Methanolic extract of *P. nitida* leaves at a dose of (300 mg/Kg) body weight tested in mice following streptozotocin induction exhibited significant antidiabetic activities with 39.40% glycaemia reduction. The measurement of stress markers in plasma, liver and kidney after administration of the extract showed significant reduction in MDA and hydrogen peroxide levels, coupled with a substantial increase in catalase activity. The plant extract is rich in polyphenolic content which attributes to the significant free radical scavenging, hypoglycaemic activity and their ability to prevent oxidative stress in diabetic rats

***Pilea microphylla* [56]**

The study revealed that the presence of flavonoids in *P. microphylla* enriched fraction (PM1) exhibited glucose lowering effect in high fat STZ induced diabetic mice.

The study has shown that PM1 at a dose of 100 mg/kg body weight for 28 days significantly reduced elevated blood glucose level which assesses its long term effect. It also inhibited DPP-IV enzyme, which is responsible for degradation of incretins such as GLP-1.

***Polygonatum odoratum* [57]**

The antihyperglycemic activity of n-butanol fraction of *P. odoratum* rhizomes have been revealed on the basis of their effect on glucose uptake in HepG2 cells and STZ-induced diabetic rats. Saponin-rich fraction significantly ameliorated clinical symptoms of diabetes including the elevated blood glucose, body weight loss as well as the increased food and water intake.

***Pseudarthria viscida* [58]**

The antidiabetic activity of ethanolic extract of *P. viscida* whole plant on Streptozotocin Nicotinamide induced type-II diabetes in rats was evaluated. The fasting blood glucose of the group treated with 200mg/kg body weight extract lowered from 210.34 mg/dl to 142.06 mg/dl and Glibenclamide from 196.5 mg/dl to 110.3 mg/dl representing 31.8% and 43.8% reductions respectively. SGOT and SGPT levels were decreased ($P<0.01$, $P<0.05$). Lipid profile was also decreased significantly ($P<0.01$, $P<0.05$). The extract produced its hypoglycemic activity by a mechanism independent from the insulin secretion, it may be by inhibition of endogenous glucose production or by the inhibition of intestinal glucose absorption.

***Psidium guajava* [59]**

The study has been performed to evaluate the antihyperglycemic and antioxidant potential of *P. guajava* fruit on STZ-induced diabetic rats. It has revealed the ripe fruit with a blood glucose lowering effect in diabetic rats at a dose of 125 and 250 mg/kg body weight. It also possesses antioxidative activity. It is postulated that it prevents the loss of islet β-cells viability and functionality against oxidative damage induced by STZ.

***Psidium guajava* [60]**

Antidiabetic and antidiarrhoeal activities of ethanolic extracts (1.00, 0.50 and 0.75 g/kg) of *P. guajava* leaves were evaluated in alloxan induced diabetic rats. The extracts were effective to decrease blood glucose level with increasing exposure time, 1g/kg body weight showing the most effective results. Guajava leaf extract has also been effective in hyperactive gut disorders.

***Retama raetam* [61]**

The antidiabetic potential of *R. raetam* fruits on STZ-induced diabetic rats have been demonstrated with extract dose of 250 and 500 mg/kg body weight respectively. The study has shown that insulin level was increased with highest extract dose of 500 mg/kg body weight which contraindicates the earlier report (Maghrani *et al.*, 2005) of inability of the extract in sensitizing insulin release. In vitro studies were performed which indicated inhibition of glucose absorption by the rat isolated intestine. The antidiabetic activity may be attributable to stimulation of insulin release due to alkaloids-induced blockade of ATP-sensitive potassium channels in β-cells.

***Sphaeranthus indicus* [62]**

The oral administration of ethyl acetate, methanolic and hydroalcoholic extracts of *S. indicus* at doses of 200 mg/kg/day for 15 days, produced significant anti-hyperglycemic action in alloxan induced diabetic rats. All the three extracts significantly lowered the elevated blood glucose levels which was comparable to glibenclamide (10mg/kg). Extract reduced oxidative stress in animals which is responsible for antidiabetic activity by its antioxidant property.

***Streblus asper* [63]**

Petroleum ether extract of *S. asper* (PESA) and α-amyrin acetate isolated from Streblus asper were screened for their antidiabetic properties in streptozotocin (STZ) induced diabetic rats. Twenty four hours after STZ induction, respective groups of diabetic rats received PESA (100, 250 and 500 mg/kg, body weight.) and α-amyrin acetate (25, 50 and 75 mg/kg, body weight.) respectively, orally daily for 15 days. Glibenclamide (0.5 mg/kg, orally) served as a reference. PESA significantly ($p < 0.01$) normalized blood glucose levels and serum biochemical parameters as compared with those of STZ controls. α-Amyrin acetate (75 mg/kg, body weight.) exhibited maximum glucose lowering effect (71.10%) in diabetic rats compared to the other dose (25, 50 mg/kg) at the end of the study. The protective effect was further confirmed by histopathological examination of the liver.

***Symplocos cochinchinensis* [64]**

The antidiabetogenic activity of hexane extract of *S. cochinchinensis* leaves has been performed. It is found to show significant reduction in increased blood glucose level at a dose of 250 and 500 mg/kg body weight in high fat diet-low STZ induced type 2 diabetic rats. Insulin tolerance test is performed and the results are expressed as 14.32% and 20.24% reduction in plasma glucose level. The hypoglycemic activity may be attributed to modulated insulin secretion by protecting against β cell damage.

***Syzygium alternifolium* [65]**

The Fraction C has been isolated from *S. alternifolium* seeds using fractionating bioassay. The study has

revealed that the daily administration of fraction C into STZ induced diabetic rats even at a low dose of 50 mg/kg body weight resulted in significant reduction of blood glucose level compared to standard drug glibenclamide (20 mg/kg body weight) without causing significant hypoglycemic state in the treated rats. It also possesses the hepatic and renal protective action against STZ induced liver damage. The antihyperglycemic and antihyperlipidemic activity may be due to increased pancreatic secretion of insulin from existing β cells and the alterations in carbohydrate and lipid metabolism.

***Taxus cuspidate* [66]**

Oral administration of crude polysaccharides (TCPs) obtained by hot water extraction and ethanol precipitation from the *T. cuspidate* at different doses of 50, 100 and 200 mg/kg body weight had an effective hypoglycemic effect in streptozotocin induced diabetic mice which were comparable to glibenclamide. Polysaccharide could effectively alleviate the impaired oxidative stress in the kidney and liver of the diabetic rats induced by STZ. Body weight loss was observed in STZ-induced diabetic mice and was returned back to normal by the treatment. The activity of the compound have been implied to its free radical scavenging potential and hence it has the ability to prevent diabetic associated complication.

***Terminalia bellerica* [67]**

Gallic acid has been isolated from *T. bellerica* fruits. The study has shown alleviation of hyperglycemia in STZ induced diabetic rats at doses of 5, 10 and 20 mg/kg body weight respectively with isolated gallic acid. Elevated levels of plasma creatinine, urea and uric acid were also reduced after treatment with isolated Gallic acid thereby assessing its potential in preventing diabetic nephropathy. The antidiabetic activity may be attributable to increase in plasma insulin and C-peptide level.

***Thymus quinquecostatus* [68]**

Antioxidant, antimicrobial, and antidiabetic activities of methanol extract of *T quinquecostatus* and those of its partitioned fractions, including hexane, ethyl acetate, n-butanol, and aqueous fractions were evaluated. Antioxidant activities of the extract were measured by 1,1-dephenyl-2-picryl-hydrazyl free radical scavenging and reducing power assay. The antidiabetic activity was evaluated by glucosidase and amylase inhibition assays. The results suggested that the ethyl acetate fraction of the methanolic crude extract possess strong antioxidant activity. In addition, ethanolic fraction showed remarkable antimicrobial activity against *Kocuria rhizophila* (MIC = 63 µg/ml) and *Staphylococcus epidermidis* (MIC = 63 µg/ml). The findings also indicated that the methanolic crude extract and its ethyl acetate fraction contained strong antidiabetic activity.

***Vernonia amygdalina* [69]**

It was revealed that co- administration of ethanolic extracts of leaves of *V. amygdalina* and *A. indica* at dose of (200 mg/kg, 50:50) possessed increased antidiabetic activity when compared with single extract in streptozotocin-induced diabetic rat models. The extracts showed synergistic activity exerted via fine glucose regulation, oxidative stress attenuation, insulin mimetic action and probable cell regeneration.

***Woodfordia fruticosa* [70]**

The hypoglycemic potential of ethanolic flower extract of *W. fruticosa* has been evaluated. The study has shown that ethanolic extract at doses 250 and 500 mg/kg significantly increases the insulin level in STZ induced diabetic rats. The antihyperglycemic effect of the extract may be attributable to its antioxidant efficacy and ability to regulate glucose homeostasis.

CONCLUSION

Diabetes is an enormous burden on patients, families, and the health care system. The epidemic increase in the number of people diagnosed with diabetes forecast year after year for the next half century, coupled with its enormous burden of cost, both fiscal and physical, threaten not only the individuals of our society but also the healthcare of our society. Based on the traditional knowledge of plants and modern technologies, different types of oral hypoglycemic agents are now available along with insulin for the treatment of diabetes mellitus. The present review has presented comprehensive details on some of the recent activities performed in traditionally claimed antidiabetic plants from various parts of the world that are used in the treatment of diabetes mellitus. The bioactive extracts of such plants along with some of the potent phytoconstituents and compounds isolated from them have been summarized and pharmacological studies performed on the experimentally induced diabetic animals have been reported. It is supposed that the review will serve to help to undertake further research regarding these plants and isolate the active compounds with antihyperglycemic property to develop potent and novel antidiabetic compounds in the future.

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