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A Review on Ethno-pharmacology of Antidiabetic Plants

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MAO and KOG designed the study. Authors MAO and OMO wrote and monitored the manuscript. Authors JOO and IFA implemented the experimental settings and processes. Author OJO carried out the literature searches and author VIE supervised the entire work. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Abnormally emanates from difficulty in insulin secretion, Diabetes mellitus (DM) is known to be a metabolic disorder that causes an increase of blood glucose in blood streams. The lack of effective modern treatments, the lifelong treatment with modern medicines, overtime, its associated health side effects, and its expensive prices among others are the challenging existing realities that devastate the health and economic burdens its sufferers, especially in developing nations. Today,

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this has prompted the search for cheap, safe, and reliable drugs from medicinal plants. This study reviewed existing information on medicinal plants used for the treatment of diabetes mellitus from various sources. Several documents (published and unpublished papers, books among others) were consulted in compilation of this review. It is found that there is a wide, yet uneven support for active components of major medicinal.

Keywords: Diabetes; prevalence; medicinal plants; ethnobotany; anti-diabetics.

1. INTRODUCTION

In 2012 there were 1.5 million deaths worldwide directly caused by diabetes. It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women [1]. World Health Organization estimates that, globally, 422 million adults aged over 18 years were living with diabetes in 2014 [1]. The term "Diabetes mellitus" (DM) is derived from the Greek words dia (through), bainein (to go) and therefore diabetes means to pass through. The disease results weight loss as if the body mass is passed through the urine [2]. The disease is defined as an elevated blood glucose associated with no or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action [3]. Besides hyperglycaemia several other factors like enhanced oxidative stress and hyperlipidaemia play a significant role in diabetic pathogenesis. The disease is progressive in nature and is associated with high risk of complications [4].

2. EPIDEMIOLOGY OF DIABETICS

There are variations in populations and among age groups of the same population in the prevalence and incidence of diabetes. According to the reports of IDF 2015, the world wide prevalence is 1 in 11 adults. More than 415 million of people have diabetes which is estimated to rise to 642 million in 2040. Among these, Africa accounts 14.2 million diabetic patients which in 2035 are likely to increase up to 34.2 million, and death of 5.0 million from diabetes in 2015. In Ethiopia, 1.3 million adult diabetic patients were identified of the age group of 20-79 years, with the prevalence of 2.9%. This figure is estimated to reach 1.8 million by 2030 [5]. Recent community based study shows the prevalence of diabetics in Ethiopia was 6% [6]. Several risk contributing factors to type II diabetes include: family history of diabetes, the demographic and behavioural factors (area of residence, age group, adding salt to food, not engaged in vigorous physical activity, alcohol consumption, chewing chat) and biological risk factors (raised BP or currently on medication or impaired glucose tolerance (IGT)). These things are significantly associated ($p<0.001$) with overweight, high blood glucose, being history of gestational diabetes and malnutrition during pregnancy and many other [6,7].

3. RELEVANCE OF MEDICINAL PLANTS AND TRADITIONAL MEDICINES IN DIABETICS

Several oral hypoglycaemic drugs like sulfonylurea, biguanides, and thiazolidenediones are commonly used for type 2 diabetes mellitus treatment, in orthodox medicine. Metformin, which is an old and widely used first-line agent, is known for its anti-hyperglycaemic properties and is also reported to improve lipid profile, fat redistribution [8], chronic liver diseases [9] and lowering of microvascular and macrovascular complications associated with diabetes mellitus [10]. There are only a few reports of induce hepatocellular and cholestatic hepatic injury [11] and hepatotoxicity [12].

Medicinal plants have been employed virtually in all cultures as a source of medicine. In developed and developing countries, around 80-85% of population rely on traditional medicine for primary health care needs. A major part of traditional therapy involves the use of plant extracts or their active principles [13]. In developing countries, lack of organized health care systems, diabetic patients are among the worst sufferers. As a result, majority of the populations still have limited or no access, (especially in remote areas) to modern medicines. Instead, for different diabetic complications they use traditional medicines [14]. The active principles of many plant species are isolated for direct use as drugs, lead compounds or pharmacological agents. Different medicinal plant species are used for the treatment of diabetes mellitus. Before the discovery of insulin by Banting and Best in 1922, the only options for diabetes treatment were based on traditional practices [15]. Till date, metformin is the major orthodox drug approved for the treatment of non-

insulins dependent diabetes mellitus patients. It is derived from a medicinal plant *Galega officinalis* [16].

4. MECHANISMS OF ACTION OF ANTIDIABETIC BOTANICALS

Antidiabetic botanicals have been reported to foster protection via several mechanisms. These include anti-inflammatory and anti-atherogenic effects; amelioration of oxidative stress, control of metabolic fluxes among various organs and energy metabolism within individual tissues and cells leading to the maintenance of glucose and lipid homeostasis and stable levels of energy stores; inhibition of aldose reductase; cyto-protection of pancreatic β-cells; improvement of endothelial dysfunction; inhibition of angiogenesis and the regulation of the expression of Antidiabetic Botanicals and their Potential Benefits in the Management of Diabetes Mellitus genes relevant for the development of T2DM. A number of candidate genes in humans and many phytochemicals/extracts from traditional medicinal plants that can target diabetogenic genes have been identified [17,18]. Medicinal plants can delay or inhibit glucose absorption, stimulate insulin secretion by the pancreas or facilitate the entry of glucose into cells such as muscle cells. Oral administration of the ethanolic extract of *Allium sativum* showed significant antidiabetic effect in normal and alloxan-induced diabetic rats and that this effect may mediate through the stimulation of insulin secretion from the pancreas [19]. Oral administration of *Gymnena sylvestre* to diabetic rats was reported to increase the number of pancreatic islet cells as well as insulin levels, which suggested a possible repair or regeneration of the pancreas. *In vitro* and *in vivo* studies showed that water soluble extracts of *Gymnena sylvestre* released insulin probably due to the regeneration of pancreatic beta cells [20]. Aqueous extract of unripe fruit of *Momordica charantia* showed partial stimulation of insulin release from isolated beta cells of obese hyperglycaemic mice which is an indication of its insulin releasing action as a result of perturbations of membrane functions [21]. *Parinari excels* showed hypoglycaemic effects due to its insulin secretory activity in diabetic animal models [22]. Epicatechin, an active principle extracted from the bark of *Pterocarpus maruspium* showed a restorative and protective effect on beta cells of diabetic subjects. This may be due to its ability to regenerate beta cells [20]. Aqueous extract of *Citrullus colocynths* showed a dose-dependent increase in insulin released from isolated islets [20]. Immunohistochemistry studies [23] showed that when compared with the control group, the amount of insulin in beta cells of the islet of Langerhans is greater in *Citrullus colocynthis* treated rats. I*n vitro* assays on some medicinal plants showed that they possess inhibitory activity on alpha glucosidase enzyme. In a study, thirty seven of forty-five samples examined showed IC_{50} values of between 2.33 *μ*g/mL and 112.02 *μ*g/mL, which were lower than that of acarbose (117.20 *μ*g/mL). Also, 80% ethanol extract from *Antidesma celebicum* leaves (Euphorbiaceae), *Garcinia daedalanthera* Pierre. leaves (Clusiaceae), *Willughbeia tenuiflora* leaves (Apocynaceae) and *Amaracarpus pubescens,* (Rubiaceae) had the highest *α*-glucosidase inhibiting activity with IC_{50} of 2.34 *μ*g/mL, 2.33 *μ*g/mL, 8,16 *μ*g/mL and 3.64 *μ*g/mL, respectively. Meanwhile, types of enzyme inhibition mechanism from *Garcinia kydia* leaves (Clusiaceae), *Amaracarpus pubescens* leaves (Rubiaceae) and *Antidesma celebicum* leaves (Euphorbiaceae) were non-competitive inhibitor, mixed inhibitor and competitive inhibitor respectively.

5. MEDICINAL PLANTS EXPLORED AS ANTI-DIABETICS

***Acacia Arabica*:** In India, *Acacia Arabica* (aka babhul) is used as home remedy medicine for reducing diabetic complications. This plant extract acts as an anti-diabetic agent by acting as secretagouge to release insulin. It resulted in hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of *Acacia arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits, induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells [24].

***Adansonia digitate*:** Every part of this plant is useful as food and for medicinal purposes in several African regions. And specifically for its medical implications, it is named “the small pharmacy or chemist tree. Hypoglycaemic activity of methanolic stem bark extract of *Adansonia digitata* in Wister rats has been investigated in streptozotocin induced diabetes. Treatment of streptozotocin-induced diabetic Wister rats with the extract caused a significant reduction in the blood glucose levels when compared with control [25]. The results suggest

that the methanolic stem bark of *Adansonia digitata* possesses antidiabetic effect on streptozotocin induced diabetic Wistar rats.

***Anacardium occidentale*. (*Anacardiaceae*):** its origin is Brazil; it is used as 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 leaves of this herb 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 animal [26].

***Annona squamosa*. (*Annonaceae*):** also known as custard apple in English and sharifa in Hindi. The pharmacological active ingredients are present in seeds, leaves and aerial parts of the plant. It was found that the plant possesses both hypoglycaemic 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 [27].

***Annona muricata*. (*Annonaceae*):** this is a 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 immune-histochemical and biochemical effects of aqueous extract of leaves on pancreatic β cells of STZ (streptozotocin) treated diabetic rats. *A. muricata*. 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 immune-reactive β-cells and partially prevents degeneration of β-cells [28].

***Adhatoda vasica*:** A research done on this plant using methanol extract from the leaves showed a sucrase inhibitory activity with sucrose as a substrate. Compounds vasicine and vasicinol showed a high sucrase inhibitory activity, and the IC_{50} values were 125 μM and 250 μM, respectively. Kinetic data revealed that the compounds vasicine and vascinol inhibited sucrose-hydrolysing pronounce activity of rat intestinal α-glucosidase competitively with *K*i values of 82 μM and 183 μM, respectively. This is the first report on the mammalian α-glucosidase inhibition of *A. vasica* and the inhibitory effect on sucrase by vasicine and vascinol from this herb species. These results suggest the use of the extract of *A. vasica* as an antidiabetic agent and also show the possibility that the compounds, vasicine and vascinol could be a useful treatment for metabolic disorders [29, 30].

***Aegle marmelos*:** *Aegle marmelos* leaf extract is being used in Indian system of medicine as an antidiabetic agent. A methanolic extract of *Aegle marmelos* was found to reduce blood sugar in alloxan induced diabetic rats. Reduction in blood sugar could be seen from 6th day after continuous administration of the extract and on 12th day sugar levels were found to be reduced by 54%. This result indicates that *Aegle marmelos* extract effectively reduced the blood glucose in diabetes induced by alloxan and it also showed antioxidant activity [31].

***Aloe barbadensis*:** This plant 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. It has been found that extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats. Treatment with prolonged but not single dose of exudates of Aloe barbadensis leaves showed hypoglycemic effect in alloxanized diabetic rats. Single as well as prolonged dose 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 [31].

***Aloe camperi*:** It was found that the methanolic extract resulted in a dose-dependent lowering of FBG levels and the result exhibited very significant (P<0.001) decreases in FBG level by the end of the experimental day as compared to the diabetic control. An Oral glucose tolerance test (OGTT) on normal rats also indicated that the hyperglycemia with glucose challenge was significantly brought down (P<0.001) by the plant extract at 60 and 120 min relative to the negative control. The methanol leaf extract of Aloe

camperi also showed a fall in blood glucose after oral administration of the extract in normal rats. This might be attributed to the presence of hypoglycemic bioactive molecules like flavonoids, terpenoids, alkaloids or saponins contained within the leaf plant [32].

***Aloe vera*:** *Aloe vera* is a well-known species of aloe, a desert plant resembling cactus. The dried sap of *Aloe vera* is a traditional remedy used in DM management in the Arabian Peninsula. Aloe gel obtained from the inner portion of the leaves contains glucomannan, a hydrosoluble fibre which has a glucose-lowering effect. This has been investigated in both animal models and type 2 DM patients. Oral administration of the juice has also been reported to reduce fasting blood glucose and triglyceride levels in type 2 DM patients with or without a combination of conventional anti-diabetic agents. No adverse effects have been reported [33].

Andrographis paniculata: The chloroform extract of Andrographis *paniculata* roots has been tested for its anti-hyperglycaemic activity in alloxan-induced diabetic rats using chronic and acute studies. Significant decrease in blood glucose levels were observed in both acute and chronic studies. The extract significantly inhibited the induction of albuminuria, proteinemia and uremia. This study indicated a significant anti-diabetic activity with the chloroform extract of A. *paniculata* roots and supports the traditional usage of the plant by Ayurvedic physicians for the control of diabetes [34].

Anthocephalus indicus: Anthocephalus *indicus* (family, Rubiacae: Hindi name- Kadam) is an ancient Indian Ayurvedic remedy that possess antidiarrhoeal, detoxification, analgesic and aphrodisiac properties. A study was carried out to evaluate the hypoglycemic, lipid lowering and antioxidant activities in root extract of Anthocephalus *indicus* in alloxan induced diabetic rats. Oral administration of ethanol extract of root (500 mg/ kg body weight) for 21 days resulted in significant decrease in the levels of blood glucose, triglycerides, total cholesterol, phospholipid and free fatty acids. Furthermore, the root extract (100- 400µg/kg) inhibited the generation of superoxide anions and hydroxyl radicals, in both enzymic and non-enzymic systems, *in vitro*. The result of this study demonstrated hypoglycemic, lipid lowering and antioxidant activities in root extract of *A. indicus*, which could help in prevention of diabetic dyslipidemia and related diseases [34].

***Artanema sesamoides*:** The methanolic extract of *Artanema sesamoides* was tested for its antidiabetic activity in streptozotocin induced diabetic rat models. Administration of this extract significantly reduced the fasting blood glucose level and increased the glycogen level in liver, compared to a control group. The extract also diminished the elevated level of SGPT, Serum Glutamic Oxaloacetic Transaminase (SGOT), and serum alkaline phosphatase and also exhibited anti-oxidant activity. This study indicates the antidiabetic potential of *Artanema sesamoides* and provides the basis for further research to isolate and identify the active constituents responsible for the reported activities [33].

***Azadirachta indica*:** The plant has a long history of medical remedy. Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin-treated rats. The extract showed an increase in glucose uptake and glycogen deposition in isolated rat hemi diaphragm [19].

***Artemesia pallens*:** It is a member of the family Compositae. Methanolic extract of aerial parts of plants has been tested for anti-diabetic activity. In glucose fed hyperglycemic rats and also in alloxan induced diabetic rats methanolic extract (100 mg/ kg given orally) reported anti-hyperglycaemic activity. Cadinol α-Curarine, β-eudesmol, β-cubebene are responsible for anti-diabetic activity. They inhibit glucose-reabsorption or increase peripheral glucose utilization [19].

***Allium cepa*:** Hypoglycaemic activity of this Lilliaceae family member reported in either soluble fraction of onion (0.25mg/kg/p.o) in streptozotocin induced rabbits. The bulb part contains s- methyl cysteine sulfoxide; s- allyl cysteine sulfoxide has anti diabetic activity. It lowers blood glucose levels and has potent anti-oxidant activity which may account for hypoglycaemic potential. Seven compounds were isolated from the ethanol extract of the seeds of *Allium cepa,* and their structures were elucidated by physico-chemical properties and spectroscopic analysis as N-trans-feruloyl tyramine, tianshic acid, sitosterol, daucosterol, beta-sitosterol-3 beta-glucopyranoside-6'-palmitate, tryptophane and sadenine riboside [35]. It is also used in osteoporosis treatment. Anticholesterolaemic and antihyperlipidaemic activities of the drug were observed after oral administration of minced bulbs, a water extract,

the essential oil (100 mg/kg), or the fixed oil to rabbits or rats.

***Allium sativum*:** Commonly known as garlic from Alliaceae family. Antihyperglycemic activity was found when tested in ethanol, ethyl acetate, and petroleum ether extract of alloxan induced rabbits. Allicin, apigenin, allicin, s- allyl cysteine sulfoxide is responsible for hypoglycaemic activity. It has been found that ethyl acetate extract is most potent and active principle producing maximum hypoglycaemic activity due to increased insulin like activity of plasma [36]. Garlic is known to possess many therapeutic benefits as it contains varieties of effective compound that exhibits anticoagulant, antioxidant, antibiotics, hypocholesterolaemic, hypoglycaemic as well as hypotensive activity. Garlic contains chemical constituents such as alliin, volatile oils, vitamins and minerals [37].

Azardirachta indiaca: *Azadirachta indica* (Family Meliaceae) is the most useful medicinal plant in India (known as neem). It possesses antibacterial, antiarthritic, anti-inflammatory, hypoglycemic, antimalarial, antiulcer, antitumour antifungal and diuretic properties [38]. The phytochemical constituents reported are tannins, coumarin, alkaloids, stigmasterol, proteins, flavonoids, saponins polyphenols, and sugars.

***Bauhinia forficata* and *Myrcia uniflora*:** *Bauhinia forficata* (Pata de vaca), indigenous to rainforests and tropical areas of South America, has been used in traditional management of DM. It has been referred to as “vegetable insulin” in Brazil. *Myrcia uniflora*, a South American herb, has also demonstrated glucoselowering effect. No adverse effects have been reported. The glucose-lowering roles of both herbs warrant further study [39].

***Boerhavia diffusa*:** *Boerhavia diffusa* (Nyctaginaceae) is known as punarnava and is used as hepatoprotective, diuretic, and for other diseases in India. A study was designed to investigate the effects of daily oral administration of aqueous solution of *Boerhavia diffusa* leaf extract (BLEt) (200 mg/kg) for 4 weeks on blood glucose concentration and hepatic enzymes in normal rats and alloxan-induced diabetic rats. A significant decrease in blood glucose and increase in plasma insulin levels were noticed in both type of rats treated with BLEt. An oral glucose tolerance test (OGTT) was also performed in the same groups, and significant improvement in glucose tolerance in rats treated with BLEt was recorded. A comparison was made between the action of BLEt and antidiabetic drug - glibenclamide (600µg/kg). The effect of BLEt was more prominent when compared to glibenclamide suggesting it was a more potent antidiabetic agent [40,41].

Butea monosperma: This plant is also known as *Butea frondosa*, (Family Fabaceae, Hindi-Dhak, Palas) and is found throughout India. A methanol extract of *Butea monosperma* seeds, tested *in vitro*, showed significant anticonvulsive, hepatoprotective and anthelmintic activity. For traditional diabetes treating claim of *Butea monosperma*, investigations were carried out to evaluate the effects of extract from the bark of *Butea monosperma* on normal mice and alloxan induced diabetic mice. The studies showed that the crude aqueous extract exhibited statistically significant hypoglycaemic and anti-hyperglycemic activities in both types of rats respectively [42].

***Bambusa arundinasia*:** The exudate on the node of this plant has been consumed for the treatment of diabetes in Persian medicine. It exhibits a-amylase and a-glucosidase enzyme inhibitory function, as well as hypoglycemic activity via improvement of serum insulin and regeneration of pancreatic tissue and Langerhans islets. The exudate also demonstrated a significant lessening of glucose-6-phosphatase and fructose-1-6-biphophatase and also reduction in HbA1c (glycated hemoglobin), total cholesterol, and triglycerides in streptozotocin-induced diabetes [43]. The leaves possess antidiabetic activity via improvement of antioxidant function and regeneration of Langerhans islet, pancreas mtissue, hepatocyte cells and kidney glomeruli and tubule. b- Sitosterol glucoside and stigmasterol are identified compounds related to this pharmacological action [44].

***Bougainvillea spectabilis Linn.*:** It’s a member in the family Nyctaginaceae, it is a very familiar ornamental plant commonly grown in Indian gardens. *Bougainvillea* is a genus of flowering plants native to South America from Brazil west to Peru and south to southern Argentina and is noted for its antidiabetic potential. The blood glucose lowering potential of *Bougainvillea spectabilis* Willd leaf extract in streptozotocin-induced type I diabetic albino rats was reported. The ethanolic extract of the leaves has antihyperglycemic activity probably due to increased uptake of glucose by enhanced

glycogenesis in the liver and also due to increase in insulin sensitivity [45].

***Bridelia ndellensis Beille.* (*Euphorbiaceae*):** This medicinal plant is used in Cameroon against diabetes. The water and methanol extract of leaf of allied species B. ferruginea has been proved as an active hypoglycemic agent in alloxan induced diabetic rats [46]. 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 [47].

Caesalpinia bonducella: *Caesalpinia bonducella F*. (Leguminosae) is widely distributed in India and the tropical regions of the world. Four extracts (ether, petroleum ether, ethyl acetate and aqueous) of the seed kernels were prepared and tested for their hypoglycaemic potentials in normal rats as well as alloxan-induced diabetic rats. In diabetic rats, both polar extracts (ethyl acetate and aqueous) similar to glibenclamide, showed significant hypoglycaemic effect, besides, reversing the diabetes induced changes in lipid and liver glycogen levels. As far as the non-polar extracts were concerned, it was only the ether extract that showed a marginal antidiabetic activity. Since both polar extracts were, through phytochemical analysis, found to contain triterpenoid glycosides, it can be assumed that they might be the active principles contributing to the antidiabetic actions [48].

***Cassia auriculata*:** *C. auriculata* (Family: Cesalpinaceae) is a common plant in Asia, profoundly used in Ayurvedic medicine as a tonic, astringent and as a remedy for diabetes, conjunctivitis and opthalmia. It is one of the principal constituents of ‘‘*Avaarai panchaga chooranam”*- an Indian herbal formulation used in the treatment of diabetes to control blood sugar. The antidiabetic activity of aqueous extract of *C. auriculata* flowers has been documented previously. Therefore, in a study, the antidiabetic potential of aqueous and ethanolic extracts of *C. auriculata* was assessed in Alloxan induced diabetic rats. Both extracts gave significant reduction in blood glucose level because of presence of anti diabetic compounds like flavonoids and phenolic acids. The anti-diabetic potential of ethanolic extract was more than that of aqueous extract. The typical dose was found to be 0.25 to 0.5gm per kg body weight [49]. In another study it was found that *Cassia auriculata* flowers possess anti-hyperlipidaemic effect, in addition to anti-diabetic activity in streptozotocin-induced diabetic model [50].

***Cocinia Indica*:** Dried extracts of *Coccinia indica* (*C. indica*) (500 mg/kg body weight) were administered to diabetic patients for 6 weeks. These extracts restored the activities of the enzyme lipoprotein lipase (LPL) that was reduced and glucose-6-phosphatase and lactate dehydrogenase, which were raised in untreated diabetics [51]. Oral administration of 500 mg/kg body weight of *C. indica* leaves showed significant hypoglycaemia in alloxanized diabetic dogs and increased glucose tolerance in normal and diabetic dogs [52].

***Coriandrum sativum*:** This plant is a member of Umbelliferae (Apiaceae) family which has a wide range of application as food additive and medicinal remedy. In Persian medicine, the plant is called “Geshniz” or “Kozborah” and has a cold and dry nature and was used for the treatment of gastrointestinal or other disorders related to accumulation of bile or blood humors. The fruit is used for the treatment of diabetes in Persian medicine. It showed hypoglycemic activity via enhancement of insulin release from b cells and number and activity of pancreatic b cells in type 1 diabetic animals [53]. Moreover, administration of the fruits as supplement in diet and drinking water showed anti-diabetic function with elevating insulin secretion, and enhancement of the level of glucose uptake, glucose oxidation and glycogenesis in diabetic mice. In a clinical trial on 50 type 2 diabetic patients, the fruit exhibited hypoglycaemic activity with reduction of total cholesterol, triglyceride, and low-density lipoprotein cholesterol, as well as improving atherosclerotic index and cardio-protective indices [54].

***Catharanthus roseus* (*Madagascar periwinkle*):** This plant, also known as *Vinca rosea* and *Ammocallis rosea*, is found in Madagascar. In Traditional Chinese Medicine, its extracts have been used to treat DM and malaria. Crude aqueous extracts of its leaves has been shown to reduce blood glucose level in normal and diabetic rats. It has however been shown to be cytotoxic [43,44].

***Croton macrostachys*:** *Euphorbiaceae* According to a study, the hydro-alcoholic root

extract of *C. macrostachys* had shown a significant blood glucose lowering effect and improved glucose tolerance after administration of oral glucose solution. It is reported that the crude extract has maximum pharmacological effect at the dose of 300 mg/ kg and it is comparable with the standard drug glibenclamide (http://www.wjpsonline.org).

***Canavalia ensiformis* (*Leguminosae*):** Known as horse bean, native of Central America and West indies has been widely cultivated in humid tropics of Africa and Asia. The seeds have been reported to possess antihypercholesterolemic [55] and hypoglycaemic [56] activities. The effect of aqueous Antidiabetic potential of medicinal plants extract of *C. ensiformis* seeds on hyperlipidemia and hyperketonemia in alloxan-induced diabetic rats proved it as active antidiabetic herb [110]. The oral administration of aqueous extract of *C.ensiformis* seeds reduce urinary and blood glucose levels, and also elevated levels of triacylglycerol, ketone bodies and cholesterol associated with diabetes mellitus [57].

***Casearia esculenta Roxb* (Flacourtiaceae):** It is a plant with medicinal properties known as wild cowrie fruit in English. The plant is in the form of shrub distributed in South India. *C. esculenta* has been a remedy which is popular for diabetes mellitus. It has been reported that plant contains hypoglycaemic effect. *C. esculenta* root extract contain hypoglycaemic factors, which reduced blood sugar level in experimental animals. *C. esculenta* root extract has influence on protein metabolism and marker enzymes in streptozotocin-induced diabetic rats. The study revealed that *C. esculenta* root extract has the anti-hyperglycemic effect and it may elevate liver and renal damage associated with streptozotocin- induced diabetes in rats [58].

***Cassia kleinii*:** It is a member of the family Caesalpiniaceae, its medical remedy for the folk diabetic practitioners in South India is pronounced. The alcoholic extracts of leaves seem to show promising results for the development of phyto-medicines by exhibiting the antihyperglycemic activity on glucose feed hyperglycemic and alloxan-induced diabetic rats. The leaf extract of *Cassia kleinii* may not act by potentiation of insulin but it could be used in insulin independent diabetes because drug exhibited antihyperglycemic effect but not hypoglycaemic effect in fasted rats. The action of drug may be mimicking some or all of the action of insulin on the metabolism of glucose [59].

***Coccinia indica* (*Cucurbitaceae*):** It is an antidiabetic remedy used mostly by sub - Saharan Africa and Southeast Asia. Pectin isolated from the fruits of *C. indica* has hypoglycemic activity. Alcoholic extract of plant was found to be active in reducing blood glucose level, then this extract was subjected to further fractionation to evaluate its biochemical parameters effecting diabetes and results suggested toluene as an active fraction. The exact action of these principles may be due to their β-cell restorative properties against alloxan induced damage [60].

***Cocculus hirsutus* (*Menispermaceae*):** 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. Its antihyperglycemic activity has been reported using aqueous extract of leaves in alloxan-induced diabetic mice. Its antidiabetic activity may be due the lowering of serum glucose level in diabetic mice and increased glucose tolerance. The extract also prevents loss of body weight [61].

***Coscinium fenestratum Colebr* (*Menispermaceae*):** Commonly known as small tree in Western Ghats (India) and Sri Lanka. The plant has been mainly used for diabetes mellitus in the traditional, Ayurvedic and Siddha systems of medicine. Alcoholic stem extract of this plant regulates metabolism and improves antioxidant status in streptozotocin, nicotinamide-induced diabetic rats. The alcoholic extract regulates glucose homeostasis and decreased gluconeogenesis by *C. fenestratum.* The drug also has protective action on cellular antioxidant defense [62].

***Dennettia tripetala* (DT):** One such dietary plant product is *Dennettia tripetala* (Annonaceae) which is widely consumed in Southern Nigeria. It is found in the tropical rainforest region of Nigeria and sometimes in Savana areas. The hypoglycaemic activity in crude methanol seed extract of DT (CMEDT) and methanol seed fraction of DT (MFDT) measured by glucose oxidase method was increased by 47.37% and 28.72%, respectively, after 8 hours of administration. After 10 days of treatment, CMEDT and MFDT gave a good glycaemic control with the highest percentage reduction of 75.82% and 71.34% in glucose level,

respectively, which is closely compared with 79.91% in glibenclamide. Thus the study showed glucose lowering effect of the seed of *Dennettia tripetala* [63].

***Dioscorea dumetorum* (*Dioscoreaceae*):** It possesses hypoglycaemic effect, and over time been used in the treatment of Diabetics traditionally. *D. dumetorum* is commonly known as bitter yam. It is mostly found in Africa. An alkaloid present in an extract, dioscoretine, has been reported to possess hypoglycemic effect. 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 [57].

***Eugenia Jambolana*:** In India, decoction of kernels of Eugenia jambolana is used as a household remedy for diabetes. This also forms a major constituent of many herbal formulations for diabetes. Anti-hyperglycaemic effect of aqueous and alcoholic extracts show reduction in blood glucose level. The extract of *jamun* pulp showed hypoglycaemic activity in streptozotocin-induced diabetic mice within 30 minutes of administration, while the seed of the same fruit required 24 hours. 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 [64].

***Eucalyptus globules*:** It has been found that this plant has antidiabetic activity. The parts used include the bark and leaves. An aqueous extract (0.5 g/ml) of *E. globulus* increased peripheral glucose utilization in mice abdominal muscle, and stepwise enhanced insulin secretion from the clonal pancreatic β- cells. A study of the effects of the leaves on STZ induced damage in pancreatic islets on normal Wistar rats suggested that the plant ameliorates diabetic states by partial restoration of pancreatic β-cells and repair of the STZ-induced damage. This shows a beneficial effect of *E. globulus* in DM management [65].

***Ficus bengalensis*:** *Ficus bengalensis* Linn, (Family: Moraceae, common name: banyan tree). Its bark is used for the treatment of diabetes. The ethanolic extracts of the different aerial parts of *Ficus bengalensis* Linn were comparatively evaluated for their blood glucose lowering activity. Histopathology was also carried out to evaluate the betacytotropic activity of various parts of *Ficus bengalensis.* The experiment confirmed the antidiabetic activity of the plant using glibenclamide as a standard drug and also confirmed the antidiabetic profiles of various parts of *Ficus bengalensis* [66].

***Ficus racemosa*:** The glucose-lowering efficacy of a methanol extract of the stem bark of *Ficus racemosa* Linn. Family Moraceae was evaluated in both normal and alloxan-induced diabetic rats. The extract at the doses examined (200 and 400 mg/kg body weight) exhibited significant hypoglycaemic activity in both experimental animal models when compared with the control group. The activity was also comparable to that of the effect produced by a standard anti-diabetic agent, glibenclamide. This investigation established pharmacological evidence to support the folkloric claim that it is an antidiabetic agent [67].

***Ficus hispida* (*Moraceae*):** Also known as Daduri for the treatment of diabetes. It is a small tree found throughout India. Cherian et al., 1993 reported the hypoglycemic activity of *F. bengalensis* bark in normal and diabetic albino rats. It was found 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 [68].

***Gymnema sylvestre*:** *Gymnema* also improves the ability of insulin to lower blood sugar in both type I and type II diabetes. Antihyperglycaemic effect of dried leaf powder of *Gymnema sylvestre* was seen in alloxanized rabbits. The effect was reflected in the activity of gluconeogenetic enzymes and reversal of pathological changes in the liver initiated during the hyperglycaemic phase. Oral feeding of powdered leaves of *G. sylvestre* (500 mg/kg body weight) for 10 days significantly prevented IV beryllium nitrate induced hyperglycaemia in rats and normalized it in 4 days in comparison to 10 days in untreated rats [69].

***Ginkgo biloba*:** Famous in traditional Chinese medicine, a species that has survived in China for more than 200 million years and now grows throughout the world. This popular herbal

medicine is extracted from the fan-shaped leaves of the ancient *Ginkgo biloba* tree. The extract may prove useful for prevention and treatment of early-stage diabetic neuropathy. *Gingko biloba* extract improves blood flow in the nerves in peripheral tissues of the arms, legs, hands, and feet and is therefore an important medicine in the treatment of peripheral vascular disease. It has also been shown to prevent diabetic retinopathy. Dosage of the extract standardized to contain 24% ginkgo flavo-glycosides is 40-80 mg, three times per day as described by Om et al. [70]

***Glycyrrhiza glabra*:** The root has been used as antidiabetic agent in Persian medicine. Glycyrrhizic acid isolated from roots possesses antidiabetic action by improvement of insulin sensitivity, enhancement of lipoprotein lipase expression in visceral and subcutaneous adipose tissues, kidney, and heart. It also reduced serum levels of fatty acid, total cholesterol, low-density lipoprotein cholesterol and lipid deposition in type 2 diabetic rat tissue. Furthermore, glycyrrhizin an active component from the roots exhibited hypoglycaemic action with enhancement of serum insulin level and pancreatic islet cells, improvement of pancreas and kidney tissues and reinforcement of antioxidant function in diabetic rats. In an experimental study reported by long-term (9 weeks) treatment with glycyrrhizin (2.7, 4.1 g/kg diet) showed a significant improve in tolerance to oral glucose loading as well as blood insulin level in genetically diabetic KK-Ay mice, an animal model of noninsulin-dependent diabetes [71].

Ginseng species: Ginseng species include Chinese or Korean ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*Panax quiquefolius*) and Japanese ginseng (*Panax japonicas*). The roots of the herb have extensively been used for their medicinal effect. Animal studies have reported significant glucose-lowering effects in both Asian ginseng [71].

***Hemidesmus indicus*:** A study was performed to evaluate the effect of *H. indicus* extract on blood glucose with fed, fasted and glucose-loaded diabetic and nondiabetic rat models [109]. Oral administration of *H. indicus* aqueous extract to fed, fasted and glucose-loaded diabetic rats decreased blood glucose level significantly at 5 hours and restored serum electrolytes, glycolytic enzymes and hepatic cytochrome P-450-dependent enzyme systems by preventing the formation of liver and kidney lipid peroxides at the end of 12 weeks of the study period. From this study, it can be concluded that the aqueous extract of the roots of *H. indicus* at a dosage of 500 mg/kg/day exhibits significant antidiabetic activity. *H. indicus* administration also decreased liver and kidney lipid peroxidation products. On the basis of these findings, *H. indicus* could be used as an antidiabetic and antioxidant agent for the prevention and treatment of diabetes mellitus [72].

***Hibiscus rosa-sinesis*:** *Hibiscus rosa-sinesis* (*Malvaceae* ,common name:Gudhal) is a small flowering tree which is found throughout India. The flowers of *H. rosa sinesis* are reported as having potent antidiabetic action. The antidiabetic property of flowers was assessed by using the acute and sub-acute models. In both models the flowers exhibited significant antidiabetic potential in a dose and time dependent manner. The ethanol extract of flowers of *Hibiscus rosa-sinensis* at doses of 250 mg/kg and 500 mg/kg body weight significantly reduced the blood glucose level in acute model at 1, 3 and 5 hour after the drug administration and in sub acute model it reduced the blood glucose at 1, 3, 5, 7 days of treatment. This study suggests that ethanolic extract of flowers can be used as a drug both for acute and chronic complications [73].

Holarrhena antidysenterica: *Holarrhena antidysenterica* commonly known as kurchi belonging to family Apocynaceae is an indigenous drug found throughout India. In an experiment conducted to determine the effect of *Holarrhena antidysenterica* (HA) (*Holarrhena pubescens*) seed powder on albino rats. There was a significant reduction in preprandial and postprandial glucose level in diabetic rats on day 7 onwards. Hypoglycaemic activity of HA on normo-glycaemic rats was also evident particularly in postprandial state at 133.75±4.01 mg/100 ml on day 28. The glucose level in HA-treated diabetic rats significantly reduced and was 142.5±1.82 and 182.5±5.88, respectively, in fasting and fed state. HA did not have any significant effect on the total cholesterol profile of normoglycaemic rats. However, there was a significant anti-hyper-cholesterolaemic activity from day 7, which became evident from day 14 onwards in fasting and fed state and finally at 63.80±3.35 and 84.27±3.07 mg/100 ml, respectively, on day 28. There was a significant reduction in blood urea nitrogen levels of HA-treated normoglycaemic rats on day 28 [74].

***Hypoxis hemerocallidea* (*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 [75]. 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 [76].

***Justicia schimperiana*:** It belongs to *Acanthaceae family*. The ethanolic extracts from both the old and young leaves of the given medicinal plant resulted a significant (p<0.05) antihyperglycemic activity [77].

Lawsonia inermis: *Lawsonia inermis* Linn (Lythraceae), commonly known as mehndi, a common plant in Asia which has been widely used in traditional medicine as a cure for diabetes. Thus a study was initiated with the aim of evaluating the effect of *Lawsonia inermis* leaves extract on blood glucose level in alloxan induced diabetic mice. The result showed that the feeding of 0.8gm per kg body weight of inai leaves extract decreased the glucose concentration from 194 mg per dilution to normal condition after 14th day. Similar results were also obtained on total cholesterol concentration and triglycerides concentration [78].

***Lactuca sativa*:** The seed, which is traditionally known as “Khas” or “Kahoo,” has been used for the treatment of diabetes in Persian medicine. It possesses a-amylase and a-glucosidase enzyme inhibitory activity. Moreover, seeds in a polyherbal formula demonstrated anti-diabetic action through elevating serum insulin, lessening glucose-6-phosphatase, and fructose-1-6-biphophatase and also improvement of pancreatic tissue and Langerhans islets in streptozotocin-induced diabetic rats [79].

***Lantana camara*:** This flowering plant of the Verbenaceae family is native to the American tropics: Mexico, Central America and Venezuela. It is also found in Africa, Australia and India. A stearoyl glucoside of ursolic acid isolated from its leaves, showed significant blood glucose level reduction in STZ-induced diabetic rats [80]. Once daily, administration of the leaves juice (1500 mg/kg) for 14 days showed significant glucose-lowering effect in rats

***Lepidium sativum*:** The hypoglycaemic effect of an aqueous extract of *Lepidium sativum* L. (LS) seeds was investigated in normal and streptozotocin (STZ)-induced diabetic rats. The blood glucose levels were normalized 2 weeks after daily repeated oral administration of aqueous LS extract (20 mg/kg) (p < 0.001). Significant reductions in blood glucose levels were noticed in normal rats after both acute (p < 0.01) and chronic treatment (p < 0.001). In addition, no changes were observed in basal plasma insulin concentrations after treatment, either in normal or STZ diabetic rats indicating that the underlying mechanism of this pharmacological activity seems to be independent of insulin secretion. This shows that the aqueous extract of LS exhibits a potent hypoglycaemic activity in rats without affecting basal plasma insulin concentrations [81].

***Mangifera indica* (mango):** This mango species is commonly found in tropical regions. It has been used as an anti-diabetic agent in Ayurvedic and Nigerian folk medicine. The glucose lowering effect of aqueous extract of the leaves has been reported in normal and diabetic rats. The active component, 3β-taraxerol, enhances insulin induced glucose uptake through translocation of the glucose transporter, GLUT 4 [82].

***Musa sapientum* (banana):** This is a hybrid of wild seeded bananas (*Musa balbasiana* and *Musa acuminata*) found in tropical countries, especially Philippines. Aqueous and methanol root extracts have been reported to have anti-oxidant and glucose-lowering effects comparable to glibenclamide [83].

***Momordica Charantia* (Bitter melon):** *Momordica charantia* is commonly used as an antidiabetic and anti-hyper-glycaemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant were shown to have hypoglycaemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycaemic effect when administered subcutaneously to langurs and humans. Ethanolic extracts of *M. charantia* (200 mg/kg) showed an anti-hyperglycaemic and also hypoglycaemic 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 [84].

***Myrtus communis*:** The fruits, traditionally called "Murd" or "Ass," have cold and dry nature and possess antidepressant, antidiarrheal, and antidiabetic activity in Persian medicine. The leave exhibited hypoglycaemic activity via enhancement of antioxidant function in hepatic tissue of diabetic animal. It also inhibited initial hyperglycaemia in streptozotocin-induced diabetic mice. Moreover, myricetin, an isolated component from this plant, exhibited anti-diabetic action via antioxidant function, as well as improvement of kidney function in diabetic rats. In addition, a-glucosidase enzyme inhibitory activity is another antidiabetic pharmacological mechanism of this plant, which myrtucommulone D, E, C, and B are responsible for this action [85].

Meriandra dianthera*:** It belongs to the Family **(Lamiaceae).* A study has evaluated the antidiabetic activities of methanol leaf extracts of this medicinal plant by administering 200 and 400 mg/kg doses of the extract orally in diabetic induced experimental rats. The methanolic extract resulted in a dose-dependent lowering of Fasting Blood Glucose (FBG) levels and the result exhibited very significant (P<0.001) decreases in FBG level by the end of the experimental day as compared to the diabetic control. The extract at 400 mg/ kg concentration produced significant anti-hyperglycaemic effect which is comparable to standard drug. An Oral glucose tolerance test (OGTT) on normal rats also indicated that the hyperglycaemia with glucose challenge was significantly brought down (P < 0.001) by the plant extract at 60 and 120 min relative to the negative control. The methanol leaf extract of *Meriandra dianthera* also showed a fall in blood glucose after oral administration of the extract in normal rats. This might be attributed to the presence of hypoglycaemic bioactive molecules like flavonoids, terpenoids, alkaloids or saponins contained within the leaf plant [86].

***Myristica fragrans*:** A study was designed to investigate the hypoglycaemic and antidiabetic activity of seeds of *Myristica fragrans* in normoglycaemic and alloxan- induced diabetic rats. The petroleum ether extract of *Myristica fragrans* (PEMF) was administered orally in normal fasted, glucose fed (1.5 g/kg) and alloxan (120 mg/kg)- induced diabetic rats (n=5). It has been found that, oral pre-treatment with PEMF at dose of 200 mg/kg body weight induced a significant decrease in blood glucose level in alloxan- induced diabetic rats after daily treatment of PEMF for two weeks. After two weeks daily administration of PEMF, diabetic treated rats showed improvement in body weight, organ (liver and pancreas) weight, lipid profiles and haemoglobin content as compared to diabetic control rats [87].

***Murraya koenigii* (Rutaceae):** It is commonly known as Curry patta and is widely used as 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. It suppresses blood glucose level and was found to have beneficial effect on carbohydrate metabolism [88].

Ocimum sanctum: The leaves of *Ocimum sanctum* have previously been reported to reduce blood glucose when administered to rats and humans with diabetes. The effects of ethanol extract and five different fractions of *O. sanctum* leaves were studied on insulin secretion, together with the evaluation of their mechanisms of action. The ethanol extract and each of the aqueous, butanol and ethyl acetate fractions, stimulated insulin secretion from perfused rat pancreas, isolated rat islets and a clonal rat ß-cell line in a concentration-dependent manner. The stimulatory effects of ethanol extract and each of these partition fractions were potentiated by glucose, isobutylmethylxanthine, tolbutamide and a depolarizing concentration of KCl. These findings indicated that constituents of *O. sanctum* leaf extracts have stimulatory effects on physiological pathways of insulin secretion which may underlie its reported antidiabetic action [89].

***Oxalis spp*:** The fruits are traditionally known to possess antidiabetic activity in Persian medicine. *Oxalis corniculata* exhibited antidiabetic action via improvement of antioxidant enzymes and function and also a-amylase enzyme inhibitory activity, as well as reduction of serum levels of triglyceride, low-density lipoprotein and cholesterol. Dietary supplementation of *Oxalis corniculata* showed a remarkable reduce in fasting serum glucose and postprandial glucose levels of streptozotocin-induced diabetic rats. The antidiabetic activity of this dietary supplement is mediated by improvement of liver tissue antioxidant enzyme (superoxide

dismutase), and total antioxidant capacity as well as suppression of oxidative stress markers [90].

***Opuntia streptacantha*:** *Opuntia streptacantha* is found in the Western hemisphere, including the south-western US, and is commonly used for its glucose-lowering effect in Mexico. It has a high-soluble fibre and pectin content, which may affect intestinal glucose uptake, partially, accounting for its glucose-lowering actions. Trials have reported improvements in patients with type 2 DM with decreased insulin levels, suggesting enhanced insulin sensitivity and secretion [91].

***Panax ginseng* (Asian ginseng, Araliaceae):** It has been reported that the root has been used clinically in the treatment of type II diabetes throughout Asian countries. Historical records revealed that *P. ginseng* has been used clinically to treat type II diabetes. *In vitro* and *in vivo* animal studies and clinical trials support the claim that the roots of this plant possess anti-hyperglycaemic activity. The ginsenoside play important role in antihyperglycemic action and other constituents have distinct pharmacological effect on energy metabolism [92].

Phyllanthus niruri: *Phyllanthus niruri* (Euphorbiaceae, common name: bhuiamla) and found widely in India. It is used in Indian traditional system of medicine to treat a wide variety of diseases, including diabetes. Therefore antidiabetic property of *Phyllanthus niruri* was evaluated by comparing in normal, insulin-dependent diabetes mellitus (IDDM), and non-insulin-dependent diabetes mellitus (NIDDM) animals through evaluating the effects on carbohydrate and lipid metabolism and antioxidant activities [109]. The alcohol extract of *Phyllanthus niruri* produced significant antidiabetic effect in IDDM alone but lowered lipid profiles and improved body antioxidant activities in both IDDM and NIDDM animals. This investigation revealed that *P. niruri* has antidiabetic potential and its lipid-lowering effect is independent from its antidiabetic action [93].

***Pterocarpus Marsupium*:** It is a deciduous moderate to large tree found in India mainly in hilly regions. Pterostilbene, a constituent derived from wood of this plant caused hypoglycaemia in dogs showed that the hypoglycaemic 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. Marsupin, pterosupin and liquiritigenin obtained from this plant showed antihyperlipidaemic activity. 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 [94].

***Portulaca oleracea*:** The seed possesses antidiabetic activity in Persian medicine. In a clinical trial, seed powder was administrated to 16 type 2 diabetic patients. This leads to enhancement of glucagon like peptide-1 level. In addition, administration of the seeds in type 2 diabetic patients resulted in reduction of fasting and post-prandial blood glucose, serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, total and direct bilirubin, increase in high-density lipoprotein cholesterol, improvement of insulin resistance and liver function. α-Amylase enzyme and a-glucosidase inhibitory activity are among other mechanism of its antidiabetic action. Also, the aerial parts of the plant demonstrated hypoglycaemic action via improvement of insulin secretion and regeneration of diabetic endothelial dysfunction through reducing triglyceride, low-density lipoprotein cholesterol vascular tension, and systolic blood pressure, and elevating high-density lipoprotein cholesterol, as well as suppressing diabetes associated vascular inflammation in an animal model of type 2 diabetes. Moreover, its leaf exhibited antidiabetic function by activation of antioxidant enzyme and suppression of lipid peroxidation in the kidney and liver of diabetic animals [95].

***Punica granatum*:** Punica granatum is native to Persia. According to text books of Persian medicine, the flowers have been widely used for the treatment of diabetes and its complications. The flowers executed antidiabetic action through a-glucosidase enzyme inhibition and improvement of insulin sensitivity with enhancement of PPAR-g (peroxisome proliferator-activated receptor–g) and GLUT4 (insulin-responsive glucose transporter 4, the insulin-dependent isoform of GLUTs). It also elevated the activity of lipoprotein lipase as well as antioxidant function and enzymes. In addition, it reduced triglyceride, cholesterol, and low-density lipoprotein and elevated high-density lipoprotein in diabetic animals.51 Gallic acid is an active constituent responsible for antidiabetic activity. In a clinical trial on type 2 diabetic patients fruit juice showed decrease in total

cholesterol, low-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol, and total cholesterol/high-density lipoprotein cholesterol. Esmaillzadeh et al., 2004 and Malini et al., 2011 demonstrated that ellagic acid, the active phenolic component of Punica granatum, reduced plasma glucose levels and blood glycosylated hemoglobin significantly, which is mediated with increase in plasma insulin concentration, in streptozotocin-induced type 1 diabetic rats [96].

Pterocarpus marsupium: *Pterocarpus marsupium* has been used for DM management in India. The flavonoid, epicatechin, extracted from the bark of the plant has been shown toprevent β-cell damage in rats. In addition, both epicatechin and a crude alcohol extract of *Pterocarpus marsupium* have been shown to regenerate functional pancreatic β-cells in diabetic animals. They therefore have the potential to prevent induction and development of DM. On the other hand, epicatechin and catechin consist of glycosides and esters. They are flavan-3-ols, a group of flavanols with glucose-lowering properties [97].

***Pentas schimperiana*:** *Rubiaceae* Both the hydro-methanolic fresh leaf extract as well as the hydro-methanolic and aqueous dried leaf extracts of *P. schimperiana* resulted in the reduction of blood glucose as a function of time and concentration in alloxaninduced diabetic mice. Similarly, the effect of oral administration of various solvent fractions of the plant on alloxan-induced diabetic mice each at a dose of 500 mg/kg also revealed that only the methanol and aqueous fractions caused a significant reduction blood glucose level where as the chloroform and acetone fractions did not [98].

***Rosa damascena* and *Rosa canina*:** In Persian medicine, the flowers are known as “Gol-e-Sorkh” with hot and dry nature. The flower and fruits of both species possess antidiabetic activity in Persian medicine sources. Antihyperglycemic and a-glucosidase inhibitory functions of methanolic extract from Rosa damascena flowers have been proven. In an animal model of type 1 diabetes mellitus (intraperitoneal injection of streptozotocin with mg/kg concentration in Wistar rat). Methanol extract of Rosa damascena flowers could significantly inhibit hyperglycemia subsequent to high-dose maltose uptake. The fruits of *Rosa canina* exhibited reduction of serum glucose via reinforcement of antioxidant function in type 1 diabetic rats [99].

***Rubia cordifolia*:** *Rubia cordifolia* belongs to family Rubiaceae. It is a well-known ayurvedic herb popularly known as Indian Madder (English), majit or manjit (Hindi), manjishtha, aruna, chitra, raktaangi, manjusha (Sanskrit), manjeshta (Marathi), manjeeth iraani (Unani), manjitti (Siddha). The antidiabetic action of *Rubia cordifolia* Linn aqueous root extract (RCAREt) was examined in streptozotocin (STZ)-induced diabetic rat model. Serum glucose, total cholesterol and triglycerides, haematological parameters, and liver and kidney transaminases in normal, STZ diabetic, and RCAREt-treated diabetic rats were measured. The observed hyperglycaemia, hypertriglycaeridemia, enhanced transaminases of liver and kidney, hypochromic microcytic anaemia, and loss of body weight in STZ diabetic rats were normalized by RCAREt treatment, whereas the hypercholesterolemia was not rectified. These results suggest the antihyperglycaemic potential of *Rubia cordifolia* aqueous root extract and the beneficial effect of RCAREt treatment might be due to different types of active principles, each with a single or a diverse range of biological activities [100].

Swertia charantia: It is commonly called Indian gentian, and belongs to family Gentianaceae. Hexane fraction of plant has blood sugar lowering effect. Swercherin (50mg/kg) given to streptozotocin induced (35mg/kg) albino rats. Insulin releasing effect of hexane fraction of plant (250mg/kg/po) is given for 28 days in albino rats shown significant raise in glycogen. Amarogentin, swercherin, chirantin, gentiopicrin stimulates insulin release from islets of Langerhans by depleting aldehyde fuschin stained β- granules and immune stained insulin [101].

***Stevia rebaudiana*:** It belongs to the family of *Lamiaceae.* The part of the plant used is the leaf. A study showed that both the aqueous and 70% ethanolic leaf extracts of the plant resulted in a fall in blood glucose level in alloxan-induced diabetic mice as a function of concentration. However, the aqueous extract showed a better reduction towards blood glucose level as compared with the ethanol extract. (http://etd.aau.edu.et/bitstream/123456789).

***Syzygium cumini*:** This is an evergreen tree found in Sri Lanka, Nepal, Pakistan, India, America, Brazil and Caribbean islands. Alcohol extracts of the seeds were shown to significantly decrease blood glucose and urine sugar in

alloxan-induced albino rats. Aqueous leaf extract (60 to 1000 µg/ml) administered to diabetic subjects caused a dose dependent inhibition of adenosine deaminase (ADA) activity and a decrease in blood glucose level [102].

***Syzyguim cumini*:** Many parts of the plant, like fruit, seeds, bark and tea prepared from the leaves, have been used in treatment of diabetes throughout Asian countries. Anti-hyperglycaemic effect has been reported in leaves, seeds, fruits, and bark. But researchers failed to identify any blood glucose lowering effect with extracts or tea prepared from leaves of plant in normal rats and in rats with STZ-induced diabetes mellitus, and in normal volunteers. Tea prepared from leaves of *S. cumini* has no hypoglycaemic effect but, as its mechanism of action could depend on specific abnormalities with the disease, the effect in diabetes is still possible [103].

***Terminalia chebula*:** *Terminalia chebula* (Combretaceae), known as harad haritaki; is used in Ayurveda to treat the complications of diabetes. Therefore a study was designed to evaluate the anti-diabetic potential of *Terminalia chebula* fruits on streptozotocin (STZ)-induced experimental diabetes in rats. Oral administration of ethanolic extract of the fruits (200 mg/kg body weight/rat/day) for 30 days significantly reduced the levels of blood glucose and glycosylated haemoglobin in diabetic rats. Determination of plasma insulin levels revealed the insulin stimulating action of the fruit extract. Also, the alterations observed in the activities of carbohydrate and glycogen metabolising enzymes were reverted back to near normal after 30 days of treatment with the extract. Electron microscopy was also performed to evaluate the histopathological changes of pancreatic cells. It was observed that histopathological abnormalities were reversed back to near normal after the treatment. These results correlate the ethnopharmacological usage of *T. chebula* fruits against diabetic conditions [104].

***Tinospora Cordifolia*:** 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* 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 (Stanley et al., 2000). 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 body weight could elicit significant anti-hyperglycaemic effect in different animal models, its effect was equivalent to only one unit/kg body weight of insulin. 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 [105].

***Trigonella foenum-graceum* (Fenugreek):** Fenugreek or *foenum-graecum*, is a crop plant grown as a potherb and for the spice made from its seeds. The fenugreek plant grows wild from the eastern Mediterranean area to China; it is cultivated worldwide. Fenugreek is used both as a herb (the leaves) and as a spice (the seed). Pre-clinical and clinical studies have demonstrated the antidiabetic properties of fenugreek seeds. The fibre-rich fraction of fenugreek seeds can lower blood sugar levels in people with diabetes, and to a lesser extent, for lowering blood cholesterol. Additionally, the soluble fibre content of fenugreek may play a role in aiding weight control. A typical dose range is 5 to 30 g three times per day with meals. Known side effects of high doses include mild digestive distress. Fenugreek should not be used by pregnant or nursing women [106].

***Terminalia chebula*:** It belongs to the family of Combretaceae**,** has been widely used in diabetes. An herbal formulation containing *T. chebula* named TRIPHALA is traditional medicine for the treatment of diabetes. Antidiabetic and reno-protective effects of the chloroform extract of *T. chebula* Retz seeds in streptozotocin- induced diabetic rats was proved. It has potent renoprotective action [21].

***Terminalia catappa*: (Combretaceae):** The petroleum ether, methanol and aqueous extract of *T. catappa* fruits was tested on the fasting blood sugar levels and serum biochemical analysis in alloxan-induced diabetic rats. All the three extracts produced a significant antidiabetic potential at dose levels of 1/5 of their lethal doses. The extract may act by β-cells regeneration. The effect may be due to β-carotine in reducing diabetic complications like glycosylation in alloxaninduced diabetic rats [106].

***Vaccinium Myrtillus* (Blueberry):** Closely related to the European bilberry, several species

of blueberries exist—including V. pallidum and V. corymbosum—and grow throughout the United States. Its leaves are the primary part of the plant used medicinally. Use of Blueberry extract is for controlling or lowering blood sugar levels when they are slightly elevated. Results have shown the leaves have an active ingredient with a remarkable ability to help the body overcome excessive sugar in the blood. It is also a good astringent and helps relieve inflammation of the kidney, bladder and prostate. To use, steep two to three handfuls of leaves in 4 cups of hot water for half an hour. Three cups a day as a drink is sufficient as describe by Om et al. [70]

***Vitis vinifera*:** The procyanidins from seeds perform antidiabetic activity via insulinomimetic function, including upgrading glucose uptake and stimulation of insulin pathway mediators. In addition, the oligomeric proanthocyanidins from seeds possess protective activity from nerve fiber against diabetic peripheral neuropathy in type 2 diabetic mice. It has been suggested that reduction in advanced glycation end products, improvement of kidney function via diminishing interstitial fibrosis, and suppressing overexpression of oxidative stress proteins are among other pharmacological mechanisms against chronic diabetes associated complications in type 1 diabetic animals [72]. In a clinical trial on type 2 diabetic patient, polyphenol extract of fruits demonstrated elevation of insulin sensitivity index and decrease of glucose infusion rate, which indicate diminishing the cellular insulin tolerance and also suppression of diabetic oxidative stress Another clinical trial on resveratrol isolated from fruits was resulted in reduction of serum glucose level, improvement of insulin sensitivity index and suppression of diabetic oxidative stress in type 2 diabetic patient. Although, resveratrol did not show any significant effect on b-cell function and serum insulin level. Also, Pourghassem-Gargari Farzaei et al., 2011 reported that administration of the seeds caused no significant effect on serum glucose and antioxidant parameters in diabetic patient in comparison with placebo group [107].

***Withania somnifera*:** *Withania somnifera* Dunal, commonly known in Sanskrit as Ashwagandha, is a perennial plant belonging to the family Solanaceae. The pharmacological effects of the roots of *W. somnifera* are attributed to the presence of withanolides, a group of steroidal lactones. Its leaves are used in Ayurvedic and Unani systems for treatment of tumors and tubercular glands. Hypoglycaemic and hypolipidaemic effects of *Withania somnifer*a root extract (WSREt) and *Withania somnifera* leaves extract (WSLEt) were investigated in alloxan-induced diabetic rats. WSREt and WSLEt and the standard drug glibenclamide were orally administered daily to diabetic rats for eight weeks. After treatment blood glucose parameters and other serological parameters were measured. Treatment of the diabetic rats with WSREt, WSLEt and glibenclamide restored the changes of the parameters to their normal level after eight weeks of treatment, indicating that WSREt and WSLEt possess hypoglycaemic and hypolipidaemic activities in alloxan-induced diabetes mellitus (DM) rats [108,109].

6. FUTURE PROSPECTS

Natural drugs from traditional medicine are gaining popularity because of several advantages such as fewer side-effects, better patient tolerance, relatively less expensive and acceptance due to a long history of use. The more important cause is that natural products, especially herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine. Therefore, a revival of interest in the use of plants in pharmacy would result in worldwide usage that emerges from both the pharmaceutical industry as a source of new lead molecules and the general public who are using plant extracts in many ways in conventional and complementary therapies. From aristocrats to common people, it was well known that natural medicines with different functions could be used to protect their health. A large number of plants were always used as folk herbs and secret recipe for different illnesses. These plants often exert a distinctive effect for some diseases including diabetes mellitus [110-112]. So, it would be interesting to discover new lead compounds for future drug development from the plants mentioned above. A special focus should be on encouragement of the folk herbs and folk therapies for the treatment of diabetes and other diseases. Although chemical and biochemical hypoglycemic agents, e.g., insulin, tolbutamide, phenformin, troglitazone, rosigitazone and repaglinide, are the mainstay of treatment of diabetes and are effective in controlling hyperglycemia, they have prominent side-effects and fail to significantly alter the course of diabetic complications. Plants have yielded directly or indirectly many important medicines in the past. For diabetes, for example, the discovery of the

widely used hypoglycemic drug, metformin, came from the traditional approach of using *Galenga officinalis*. The traditional Chinese medicines, all of which come from nature products, are thought to treat diabetes through improving the immunity of the body. These traditional Indian medicines have great potential for scientists to find active compounds and develop new medicine for diabetes mellitus [113].

7. CONCLUSION

Diabetes is a metabolic disorder. It is predicted that the number will increase to over 366 million by the year 2030 and also this number will increase in developing countries. In the present review an attempt has been made to investigate the antidiabetic medicinal plants used in the treatment. This review article may be useful to the professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop antidiabetic drugs. Hence medicinal plants are the best alternative for the treatment of diabetes mellitus. 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 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 among others 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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