American Journal of Pharmacological Sciences, 2015, Vol. 3, No. 3, 55-66
Available online at http://pubs.sciepub.com/ajps/3/3/2

DOI:10.12691/ajps-3-3-2

Plants Explored with Anti-diabetic Properties: A Review

Om Prakash[1], Rajesh Kumar[1], Ritika Srivastava[1], Pragya Tripathi[1], Shradha Mishra[2], Ajeet[3,*]

[1]Faculty of Pharmacy, Kamla Nehru Institute of Management & Technology, Sultanpur, Uttar Pradesh
[2]Faculty of Pharmacy, Sagar Institute of Technology & Management, Barabanki, Uttar Pradesh
[3]S. D. College of Pharmacy and Vocational Studies, Muzafffarnagar, Uttar Pradesh, India
*Corresponding author: ajeet_pharma111@rediffmail.com

Received May 03, 2015; Revised May 20, 2015; Accepted May 24, 2015

Abstract Diabetes mellitus is a chronic heterogeneous disorder; affecting the β-cells of endocrinal pancreatic gland, globally the numbers of cases of diabetes is increasing gradually. There are several medicines available in the market to treat diabetes mellitus but no drug is found to be fully effective and safe. However plants and plant-derived products have proven to be effective and safe in the treatment of various types of diabetes mellitus. In Indian system of medicine, several medicinal plants have found potential use as blood sugar lowering agents. Many of them have been scientifically explored for their usefulness in managing diabetes, the reports of which have been acknowledged and published in a number of scientific journals. At present most research work on diabetic drugs is targeted on plants and plants-derived products. Many natural products and their analogues have been identified as potent anti-diabetic agents. Here, an attempt is being made through this article to provide an in-depth and comprehensive review on various plant species that have been explored as anti-diabetic agents.

Keywords: *diabetes mellitus, insulin, natural products, glucose*

Cite This Article: Om Prakash, Rajesh Kumar, Ritika Srivastava, Pragya Tripathi, Shradha Mishra, and Ajeet, "Plants Explored with Anti-diabetic Properties: A Review." *American Journal of Pharmacological Sciences*, vol. 3, no. 3 (2015): 55-66. doi: 10.12691/ajps-3-3-2.

1. Introduction

1.1. Diabetes Mellitus

Diabetes mellitus is a metabolic disorder initially characterized by a loss of glucose homeostasis, due to disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin production, secretion, insulin action [1]. This can result in long-term damage to organs, such as the kidneys, liver, eyes, nerves, heart and blood vessels. Complications in some of these organs can lead to death [2].

1.2. Pathophysiology of Diabetes Mellitus

The pancreas plays a primary role in the metabolism of glucose by producing and secreting the hormones like insulin and glucagon. The islets of Langerhans produce and secrete insulin and glucagon directly into the blood. Insulin is a protein that is essential for proper regulation of glucose and for maintenance of proper blood glucose levels [3]. Glucagon is a hormone that opposes the action of insulin. It is secreted when blood glucose level falls. It increases blood glucose concentration, partly by stimulating the breaking down of stored glycogen in the liver by a pathway known as glycogenolysis. Gluconeogenesis is the production of glucose in the liver from non-carbohydrate precursors such as glycogenic amino acids [4].

1.3. Types of Diabetes Mellitus

WHO classification of diabetes introduced in 1980 and revised in 1985 was based on clinical characteristics. The two most common types of diabetes were insulin-dependent diabetes mellitus (IDDM) or (type I) and non-insulin-dependent diabetes mellitus (NIDDM) or (type II). WHO classification also recognized malnutrition-related diabetes mellitus and gestational diabetes. Malnutrition-related diabetes was omitted from the new classification because its etiology is uncertain, and it is unclear whether it is a separate type of diabetes [5,6].

1.3.1. Type I Diabetes Mellitus

It is a result of cellular mediated autoimmune destruction of the insulin producing and secreting β-cells of the pancreas, which results in an absolute deficiency of insulin for the body. Patients are more prone to ketoacidosis. It usually occurs in children and young adults, usually before 40 years of age, although disease onset can occur at any age. The patient with type I diabetes must rely on insulin medication for survival. It may account for 5 -10 % of all diagnosed cases of diabetes [7]. Autoimmune, genetic and environmental factors are the major risk factors for type I diabetes [7,8,9,10].

1.3.2. Type II Diabetes Mellitus

Two key features in the pathogenesis of type II diabetes mellitus are a decreased ability of insulin to stimulate glucose uptake in peripheral tissues, insulin resistance,

and the inability of the pancreatic β-cell to secrete insulin adequately, β-cell failure. The major sites of insulin resistance in type 2 diabetes are the liver, skeletal muscle and adipose tissue [11]. Both defects, insulin resistance and β-cell failure, are caused by a combination of genetic and environmental factors. Environmental factors such as lifestyle habits (i.e., physical inactivity and poor dietary intake), obesity and toxins may act as initiating factors or progression factors for type II diabetes. The genetic factors are still poorly understood [5,7,12,13,14].

1.4. Gestational Diabetes Mellitus

Gestational diabetes, blood glucose elevation during pregnancy, is a significant disorder of carbohydrate metabolism due to hormonal changes during pregnancy, which can lead to elevated blood glucose in genetically predisposed individuals. It is more common among obese women and women with a family history of diabetes. It usually resolves once the baby is born, however, after pregnancy, 5-10% of women with gestational diabetes are found to have type II diabetes and 20-50% of women have a chance of developing diabetes in the next 5-10 years [3,4,5,6,7].

1.5. Prevalence and Incidence of diabetes Mellitus

The prevalence of diabetes mellitus, especially type II, is increasing with ageing of the population and lifestyle changes associated with rapid urbanization and westernization. The disease is found in all parts of the world and is rapidly increasing in its coverage [15,16]. Globally, the prevalence of diabetes (Table 1), without type distinction, was estimated to be 4% in 1995. According to WHO, it is estimated that 3% of the world's population have diabetes and the prevalence is expected to double by the year 2025 to 6.3% [17,18]. There will be a 42% increase from 51 to 72 million in the developed countries and 170% increase from 84 to 228 million, in the developing countries. Thus, by the year 2025, over 75% of all people with diabetes will be in the developing countries, as compared to 62% in 1995 [19]. The reasons behind this projected increase in prevalence rate are due to urbanization, westernization and their associated lifestyle changes, increase in life expectancy at birth, physical inactivity and obesity and possibly a genetic predisposition [16,20]. Age, ethnic, regional and racial differences have also been found to play a role for the diabetic incidence in heterogeneous populations within the same area [21,22,23].

Table 1. Worldwide prevalence of diabetes [5]

Prevalence (n x 10^6)			Increase (%)
Geographical Region	**2003**	**2025 (Predicted)**	
Africa	13.6	26.9	98
Asia	81.8	156.1	91
Australia	1.1	1.7	59
Europe	38.2	44.2	16
Middle East	18.2	35.9	97
North America	25.0	39.7	59
South America	10.4	19.7	88
Total cases worldwide	189	324	72

2. Importance of Medicinal Plants and Traditional Medicines

Medicinal plants, since time immemorial, have been used in virtually all cultures as a source of medicine. It has been estimated that about 80-85% of population, both in developed and developing countries rely on traditional medicine for their primary health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles [24,25,26]. Due to lack of organized health care systems in developing countries, people with chronic diseases like diabetes are among the worst sufferers in their communities today. Hence, majority of the populations still have limited access or no access, especially those in remote areas, to modern medicines. Instead they use traditional medicines for a range of diabetic complications [27,28]. The active principles of many plant species are isolated for direct use as drugs, lead compounds or pharmacological agents. Different species of medicinal plants are used in the treatment of diabetes mellitus. For diabetes treatment, before the discovery of insulin by Banting and Best in 1922, the only options were those based on traditional practices [29]. Till today metformin is the major orthodox drug approved for the treatment of non insulin dependent diabetes mellitus patients. It is derived from a medicinal plant *Galega officinalis* [30,31].

3. Important Medicinal Plants Explored as Anti-Diabetic

3.1. Acacia Arabica

Acacia Arabica (babhul) is used as home remedy in Indian system of medicine for reducing the complications of diabetes. It is found that this plant extract acts as an anti-diabetic agent by acting as secretagouge to release insulin. It induces hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of Acacia arabica when administered (2, 3 and 4 g/kg body weight) to normal rabbits, induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells [32].

3.2. *Adansonia digitata*

Leaves bark and fruits of *Adansonia digitata* are traditionally employed in several African regions as food and for medicinal purposes, and for the letter use, it is also named "the small pharmacy or chemist tree [33]. Hypoglycemic 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. The dose of 100mg/kg showed a significant decrease after 1, 3, 5 and 7 hours of extract administration, compared to control normal saline. Also the dose of 200 mg/kg shown a significant decreased after 3, 5 and 7 hours of extract administration. The dose of 400 mg/kg also showed a significant decrease of blood glucose after 5 and 7 hours of extract administration, compared to control normal saline. These results suggest that the methanolic stem bark

of *Adansonia digitata* possesses antidiabetic effect on streptozotocin induced diabetic Wistar rats [33].

3.3. *Adhatoda vasica*

The methanolic extract from the leaves of *Adhatoda vasica* Nees (Acanthaceae) 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 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 [34].

3.4. *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 [35].

3.5. *Aloe barbadensis*

Aloe, a popular house 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. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats [36]. 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 [37].

3.6. *Andrographis paniculata*

The chloroform extract of *Andrographis paniculata* roots has been tested for its anti hyperglycemic activity in alloxan-induced diabetic rats using chronic and acute studies. Significant reductions in blood glucose levels were observed in both acute and chronic studies. The extract significanly inhibited the induction of albuminuria, proteinemia and uremia. This study clearly 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 [39].

3.7. *Anthocephalus indicus*

Anthocephalus indicus (family, Rubiacae: Hindi name-Kadam) is one such Ayurvedic remedy that has been mentioned in many ancient Indian medical literatures to 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 inducd 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 [39].

3.8. *Artanema sesamoides*

The methanolic extract of *Artanema sesamoides* was investigated 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, 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 [40].

3.9. *Azadirachta indica*

Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin-treated rats. The extract caused an increase in glucose uptake and glycogen deposition in isolated rat hemi diaphragm. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects [41].

3.10. *Boerhavia diffusa*

Boerhavia diffusa (Nyctaginaceae) is known as punarnava and is used as diuretic, hepatoprotective and for treatment of other diseases in the Indian medicinal system. 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 significant increase in plasma insulin levels were observed in the normal and diabetic rats treated with BLEt. An oral glucose tolerance test (OGTT) was also performed in the same groups, and there was a significant improvement in glucose tolerance in rats treated with BLEt. 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 antidaibetic agent [42].

3.11. *Butea monosperma*

The plant *Butea monosperma* belongs to the family Fabaceae. It is also known as *Butea frondosa*, (Hindi-Dhak, Palas) and is found throughout India. A methanol extract of *Butea monosperma* seeds, tested *in vitro*, showed significant anthelmintic activity, anticonvulsive and hepatoprotective. In light of the traditional claim on the use of *Butea monosperma* in the treatment of diabetes, 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 indicated that the crude aqueous extract exhibited statistically significant hypoglycaemic and anti-hyperglycemic activities in normal and alloxan-induced diabetic albino rats respectively [43].

3.12. *Caesalpinia bonducella*

Caesalpinia bonducella F. (Leguminosae) is a medicinal plant, widely distributed throughout India and the tropical regions of the world. Four extracts (petroleum ether, 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 presumed that they might be the active principles contributing to the antidiabetic actions [44].

3.13. *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 the blood sugar level. 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 [45]. 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 [46].

3.14. 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 [47]. 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 [48].

3.15. 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. This varies with the severity of diabetes. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) it is reduced to 55.62% and 17.72% respectively. 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 [49].

3.16. *Ficus bengalensis*

Ficus bengalensis Linn, commonly known as the banyan tree, belongs to the Moraceae family. 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 ethanolic extract of the fruit, at a dosage of 120 mg/kg body weight, was found to exert a more pronounced antidiabetic activity than the ethanolic extract of the root or bark. 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* [50].

3.17. *Ficus racemosa*

The glucose-lowering efficacy of a methanol extract of the stem bark of *Ficus racemosa* Linn. (Family Moraceae) was evaluated both in 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 [51].

3.18. *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 [52]. Oral feeding of powdered leaves of *G. sylvestre* (500 mg/kg body weight) for 10 days significantly prevented IV beryllium nitrate induced hyperglycaemica in rats and normalized it in 4 days in comparison to 10 days in untreated rats.

3.19. *Ginkgo biloba*

Long used in traditional Chinese medicine, a species that has survived in China for more than 200 million years and now grows throughout the world. 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 flavoglycosides is 40-80 mg three times per day.

3.20. *Hemidesmus indicus*

Hemidesmus indicus has been reported to be used as a tonic, demulcent, and diaphoretic and has traditionally been used to treat venereal diseases, skin diseases, urinary infections, negative emotions and impotence. 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. 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 [53].

3.21. *Hibiscus rosa-sinesis*

Hibiscus rosa-sinesis (Malvaceae), commonly known as Gudhal, is a flowering small 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 [54].

3.22. *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, the treatments comprised the following: normal rats orally treated with 1.5 ml saline/kg body weight (I; control); normal rats orally treated with 350 mg HA/kg body weight (II); diabetic control rats orally treated with 1.5 ml saline/kg body weight (III); diabetic rats orally treated with 350 mg HA/kg body weight (IV); and diabetic rats orally treated with 0.5 mg glibenclamide/kg body weight (V). There was a significant reduction in preprandial and postprandial glucose level in diabetic rats on day 7 onwards. Hypoglycaemic activity of HA on normoglycaemic 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 from day onwards 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 antihypercholesterolaemic 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 [55].

3.23. *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 [56].

3.24. *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. After an acute (single dose) or chronic (15 daily repeated administration) oral treatments, the aqueous LS extract (20 mg/kg) produced a significant decrease in blood glucose levels in STZ diabetic rats ($p < 0.001$). 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 [57].

3.25. Momordica Charantia (Bitter melon)

Momordica charantia is commonly used as an antidiabetic and antihyperglycaemic 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-hyperglycemic and also hypoglycemic effect in normal and STZ diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6-biphosphatase in the liver and stimulation of hepatic glucose-6-phosphate dehydrogenase activities [58].

3.26. *Myristica fragrans* (Nutmeg)

Myristica fragrans Houttuyn (Myristicaceae) is used for treating diarrhoea, mouth sores, and insomnia. 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, *p.o.*) and alloxan (120 mg/kg, *s.c.*)- induced diabetic rats (n=5). In addition, changes in body weight, organ (liver, kidney and pancreas) weight, serum lipid profile and blood parameters (hemoglobin, erythrocytes and differential whole cell counts) assessed after two weeks in the extract treated diabetic rats. 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, i) from 56.5±3.19 (0 h) to 49.75±2.05 mg% (4 h) in normoglycaemic rats, ii) from 145.75±9.65 to 81.5±4.03 mg% in oral glucose tolerance test (OGTT) at ½ h compared to control glucose fed rats, iii) from 305.8±12.49 to 276.6±6.11 mg% after single dose treatment and from 326.25±7.05 to 268.0±9.6 mg% 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 [59].

3.27. *Ocimum sanctum*

Ocimum sanctum, commonly known as tulsi is used traditionally as home remedies for various types of disorders. 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. Inhibition of the secretory effect was observed with diazoxide, verapamil and Ca^{2+} removal. In contrast, the stimulatory effects of the chloroform and hexane fractions were associated with decreased cell viability and were unaltered by diazoxide and verapamil. The ethanol extract and the five fractions increased intracellular Ca^{2+} in clonal BRIN-BD11 cells, being partly attenuated by the addition of verapamil. 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 [60].

3.28. Onion (*Allium cepa*)

Onion is a member of the lily family (Liliaceae). It is native to Eurasia but now grows all over the world, due mostly to people taking it with them as a staple food wherever they migrated. Experimental and clinical evidence suggests that onion consists of an active ingredient called allyl propyl disulphide (APDS). APDS has been shown to block the breakdown of insulin by the liver and possibly to stimulate insulin production by the pancreas, thus increasing the amount of insulin and reducing sugar levels in the blood [61].

3.29. *Phyllanthus niruri*

Phyllanthus niruri (Euphorbiaceae), is commonly known as bhuiamla and found throughout India. It is widely 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. 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 [62].

3.30. 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 [63].

3.31. *Rubia cordifolia*

Rubia cordifolia Linn belonging to family Rubiaceae is a well known ayurvedic herb popularly known as Indian Madder (English), manjeshta (Marathi), majit or manjit (Hindi), manjishtha, aruna, chitra, raktaangi, manjusha (Sanskrit) 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 anemia, 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 [64].

3.32. *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 hemoglobin 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 [65].

3.33. 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 (T. cordifolia) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight [66]. 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 [67]. 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.

3.34. *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 fiber-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 fiber 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 [68].

3.35. 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.

Table 2. Other medicinal plants reported with anti diabetic properties

S. no	*Plant*	Plant part	Extract used	Study Animal
1	*Abroma augustata*	Whole plant	Aqueous	Rats
2	*Acacia Arabica*	Seeds	Powder	Rabbit
3	*Allium cepa*	Fruit	Ethyl ether	Rabbits
4	*Allium satium*	Fruit	Ethanol.	Rabbits
6	*Annona squamosa*	Leaf	Alcoholic	Rats
7	*Artemisia pallens*	Aerial parts	Methanolic	Rats
8	*Areca catechu*	Seed	Aq., Methanolic	Rabbits
9	*Bambusa arundinacea*	Leaf	Alcoholic	Rabbits
10	*B. nutans Wall.*	Whole plant	50%Ethanolic	Rats
11	*Barleria lupulina*	Aerial parts	Methanolic	Rats
12	*Bauhinia candicans*	Leaf	Ether	Rats

13	*Bauhinia forficata*	Leaf, Flower	Aq., Ethanolic	Rats
14	*Azadirachta indica*	Leaves	Hydroalcoholic	Rats
15	*Beta vulgaris*	Root	-------	Rats
16	*Bidens pilosa*	Stem, Leaf	Butanol fraction	Mice
17	*Biophytum sensitivum*	Leaf	Methanolic	Rabbits
18	*Boerhavia diffusa*	Leaf	Alcoholic/aqueous	Rats
19	*Bombox ceiba*	Leaf	Hydroalcoholic	Rats
20	*Cacalia hastate*	------	Aqueous	------
21	*Caesalpinia bonducella*	Seeds	Alcoholic/aqueous	Rats
22	*Caesalpinia sappan*	Leaves, Flowers	-----	Rats
23	*Cajanus cajan*	Seeds	----	Mice
24	*Camellia sinensis*	Top leaves	Green tea	Rats
25	*Capparis decidua*	Fruit	-------	Rats
26	*Cassia auriculata*	Dried flowers	Methanol	Sd- rats
27	*Catha edulis*	Khat	------	------
28	*Centaurea aspera*	Flower	Aqueous	Rabbit
29	*Cinnamomum zeylanicum*	Bark	Aqueous	Rats
30	*Citrullus colocynthis*	Fruit	Aqueous	Rabbit
31	*Clitoria ternatea*	Seed bark	Aqueous	Rats
32	*Coccinia indica*	Leaves	Alcoholic	Guinia pigs
33	*Coctus afer. Ker*	Leaf	Methanolic	Rats
34	*Curcuma longa*	Rhizome	Aqueous	Rats
35	*Datura metel*	Seed powder	Aqueous	Rats
36	*Dipteracanthus prostratus*	Whole plant	50% ethanolic	Rats
37	*Dodonea viscosa linn.*	Whole plant	50% ethanolic	Rats
38	*Enicostemma littorale*	Whole plant	Methanol	Rats
39	*Eucalyptus globulus*	Leaves	Aquous	Mouse
40	*Eugenia jambolona*	Seed kernal	Hydroalcoholic	Rats
41	*Eugenia uniflora*	Leaves	Ethanolic	Mice
42	*Ficus bengalensis*	Bark	------	-------
43	*Ficus racemosus linn.*	Seeds	50% ethanolic	Rats
44	*Gymnema sylvestre*	Leaves	----------	Rabbits
45	*Helicteres isora*	Roots	Chloroform	Rats
46	*Heliotropium subulatum hochst.*	Whole plant	Ehtanolic	Albino rats
47	*Hibiscus esculentus*	Seeds	Water (Hot/cold)	Rats
48	*Hibiscus rosa sinensis*	Leaves	Ethanol	Rats
49	*Hibiscus sabdariffa linn.*	Whole plant	Ethanolic	Rats
50	*Holarrhena antidysentrica*	Fruits	50% ethanolic	Rats
51	*Hyptis suaveolens*	Whole plant	50% ethanolic	Rats
52	*Indigofera tinctoria linn.*	Whole plant	--------	Rats
53	*Inula racemosa*	Roots	-------	Mice
54	*Ipomoea batatas*	Leaves, flowers	-------	Rats
55	*Lagerstroemia parviflora roxb.*	Whole plant	50% ethanolic	Rats
56	*Lagerstroemia speciosa*	Leaf	-------	Mice
57	*Lantana camara*	Leaves	Juice	Rats
58	*Laurus nobilis linn.*	Leaf	Aqueous	Rats
59	*Luecaenaleucocephala lam.*	Seeds	-------	Rats
60	*Lupinus albus linn.*	Seed	-----	Rats
61	*Luffa echinata roxb.*	Whole plant	50% ethanolic	Rats
62	*Mallotus philippensis*	Fruit	50% ethanolic	Rats
63	*Mangifera indica*	Leaves	Aqueous	Rats
64	*Marsdenia volubilis*	Leaves	Aqueous	Rabbit
65	*Mamacylon umbellatum*	Leaves	Alcoholic	Rats
66	*Michelia champaca Linn.*	Stem bark	Ethanolic	Rats
67	*Momordica cymbalaria*	Fruit	Powder	Rats
68	*Momordica charantia*	Fruit	Ethanolic	Rats
69	*Momordica tuberose*	Fruit	Powder	Rats
70	*Morus alba*	Leaves	Aqueous	Mice
71	*Mucuna pruriens*	Seeds	Powder	Rats
72	*Murraya koeingii*	Leaves	Powder	Rats
73	*Musa sapientum*	Flower	Chloroform	Rats
74	*Myrtus communis Linn*	Leaves	Aqueous/ethanolic	Rats

75	*Nelumbo nucifera*	Rhizome	Ethanolic	Rats
76	*Neurolemma lobata*	Leaves	Ethanolic	Mice
77	*Ocimum sanctum*	Leaves	Ethanolic	Rats
78	*Orthosiphon stamineus benth*	Leaves	Aqueous	Rabbits
79	*Petroselinum crispum*	Leaves	Aqueous	Rats
80	*Phaseolus vulgaris linn*	Leaves	Aqueous	Humans
81	*Phyllanthus embelica*	Dried fruit	Methanolic	Rats
82	*Phyllanthus fraternus webster*	Leaf	Aqueous	Rabbits
83	*Phyllanthus niruri*	Whole plant	Aqueous	Rabbits
84	*Picrorrhiza kurroa*	Whole plant	Alcoholic	Rabbits
85	*Piper longum*	Whole plant	Ethanolic	Rats
86	*Piper nigrum*	Fruit	Ethanolic	Humans
87	*Plantago himalaica pilger*	Fruit	Ethanolic	Rats
88	*Plantago rubra linn.*	Stem	Ethanolic	Rats
89	*Pongamia pinnata merr.*	Stem	Ethanolic	Rabbits
90	*Premna obtusifolia*	Stem	Ethanolic	Rats
91	*Pterocarpus marsupium*	Wood	Ethanolic	Rats
92	*Pterocarpus santalinus*	Seed	Ethanolic	Rats
93	*Pterospermum semisagittatum*	Leaves	Ethanolic	Rats
94	*Pueraria lobata*	Roots	Ethanolic	Rats
95	*Punica gratum*	Flowers	Aqueous	Rats
96	*Ricinus communis*	Flowers	Aqueous	Rats
97	*Rhizophora apiculata*	Leaves	Alcoholic	Rats
98	*Rhus chinensis mill.*	Whole plant	Ethanolic	Rats
99	*Ricinus communis*	Root	Ethanolic	Rats
100	*Salacia oblonga*	Root bark	Aqueous	Rats

3.36. *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 [79].

Other medicinal plants reported with anti-diabetic properties are show in Table 2.

4. Future Prospects

Natural drugs from traditional Indian 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. In the use of several thousand years in India, the traditional Indian medicine has built up characteristics of its own in medical system. 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. So, it would be interesting to discover new lead compounds for future drug development from the traditional Indian medicines with definite functions which have not yet been worked upon or developed. 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. Some traditional Indian medicines appear to be effective for both the control of blood glucose and the modification of the course of diabetic complications without side-effects. 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

drugs for anti-diabetes. Many Simple Recipes and Compound Recipes have been shown to possess several hypoglycemic mechanisms to treat complication while lowering blood glucose; some ones even possess activity to regulate blood glucose two-dimensionally. These Indian medicines are a potential source of anti-diabetic drugs because of their remarkable efficacy, rich resources and the characteristic anti-diabetic mechanisms. The clinical practice from hospital and folk experience has shown the possibility to obtain natural products to recover diabetes and its complications from traditional Indian medicinal plants. Thus, there is an increasing requirement and the feasibility to screen and obtain active compounds including plant extracts from Indian traditional medicinal plants for the treatment of diabetes and its complications. The lack of scientific and experimental evidence about effective constituents, toxicity, pharmacokinetics, effectiveness and efficacy resulted in deficiency of belief in effectiveness, quality and safety of Indian medicines. The need for adequate standards of herbal preparations to ensure quality, safety and efficacy has been highlighted since the use of herbal medicines and phytotherapy. This requires biological testing of plant extracts, isolation of bioactive components, as well as toxicological, pharmacodynamical and, ultimately, clinical studies. For Indian medicinal preparations, which are made from plant extracts, and often considered to be effective due to a mixture of active ingredients rather than a single constituent, standardization process is difficult; furthermore, there is always a possibility of antagonism within bioactive moieties in extract which may result into loss of activity. However, the standardization is an absolute necessity for the survival of any plant based technology. It is quite a remarkable effort to isolate active components of Indian medicinal plants with confirmed hypoglycemic activity as "leads", to explain their pharmacological mechanism, and lastly, to develop conventional dosage forms which not only controls diabetes but takes care of associated complications [70,71].

5. Conclusion

Among many disease or disorders of carbohydrate, fat and protein metabolism, diabetes is a serious disorder effecting large population of the world. It is associated with decreased insulin production or resistance towards its action. Plants have been traditionally used to treat diabetes patients, both insulin dependent & non insulin dependent diabetes. They have also been reported to be used in associated conditions of diabetes like diabetic peripheral neuropathy, diabetic retinopathy etc. Recent scientifically carried out research work have justified the role of herbs in the management of diabetes, however it would be unwarranted to assure that all these plants can be blindly used in diabetic patients. Authors feel that still there these plants have to go a long way in terms assessment parameters like toxic effects, herb-herb; herb-drug interaction etc. and ongoing exploration regarding pharmacological actions and isolation of bioactive compounds should be continued. Although there is an increase in the number of patients suffering from diabetes in every age group during the last decade. Herbs are highly esteemed for millennia as a rich source of therapeutic agents for prevention and treatment of diabetes and its ailments. Although the contribution of modern synthetic medicine for elevating the human sufferings cannot be under-estimated, equally true is the fact that most of them leave unwanted harmful side/toxic effects on the human system disturbing the basic physiology? During the last three decades or so there has been serious realization of these problems associated with synthetic drugs and as a result the world has started looking towards the herbs as agents of therapy which, apart from being comparatively economical and easily available, are relatively free from the problems of side effects, toxicity and developing resistance towards causative organisms.

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