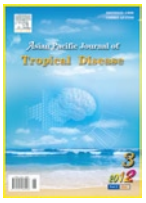
Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage:www.elsevier.com/locate/apjtd



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Natural medicines from plant source used for therapy of diabetes mellitus: An overview of its pharmacological aspects

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ARTICLE INFO

Article history:
Received 25 February 2012
Received in revised form 12 April 2012
Accepted 27 May 2012
Available online 28 June 2012

Keywords:
Antioxidant
Blood glucose
Diabetes mellitus
Herbal therapy
Insulin
Oral hypoglycemic agent
Phytoconstituent
Plant extract

ABSTRACT

Medicinal plants play an important role in the treatment of diabetes mellitus, especially in the developing countries due to their cost effectiveness. Diabetes mellitus, a metabolic disorder, is becoming a serious threat to mankind health. The prevalence of diabetes mellitus is expected to reach up to 4.4% in the world by 2030. Among all type of diabetes, type 2 diabetes is main complication. Currently available treatment options in modern medicine have several adverse effects. Therefore, there is a need to develop safe and effective treatment modalities for diabetes. In this regard, plants provide the best option for search of desired safe and effective medications. Since ancient times, plants have been an exemplary source of medicine. Various plants have been found to possess significant anti-diabetic property after their preclinical and clinical evaluation. This present review presents the profiles of plants with hypoglycaemic properties reported in the literature from 2009 to 2011. Use of these plants may delay the development of diabetic complications and can correct the metabolic abnormalities through variety of mechanisms. Moreover, during the past few years many phytoconstituents responsible for anti-diabetic effects have been isolated from plants. Since this review has been presented in a very interactive manner showing geographical region of availability, parts of plant used, mechanism of action and phytoconstituents responsible for particular action, it will be of great importance to intrested readers to easily identify and go for further research on the plant of their interest.

1. Introduction

Diabetes mellitus is chronic metabolic disorders that affect human body in terms of physical, psychological and social health. It is defined as a group of disorders characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins[1,2]. It is becoming the third "killer" of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases[3]. The prevalence of diabetes mellitus is expected to reach up to 4.4% in 2030, and the occurrence was found to be high in India, China, and USA. Historical accounts reveal that as early as 200 BC, diabetes mellitus was well recognized disease in India even as distinguished in two types: a genetically based disorder and a dietary related disorder[4]. Among all the cases of diabetes, type 2 diabetes was found to be more prevelent[5]. The pernicious effects of diabetes have been found to be mediated through oxidative stress. Oxidative stress is associated with increased production of reactive oxygen species and impaired antioxidant defense systems, which cause lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism[6]. The increased production and ineffective scavenging of reactive oxygen species may play a critical role in diabetese mellitus. Disturbance of antioxidants defence system in diabetes is mainly because of alteration in antioxidant enzymes, impaired glutathione metabolism, and decreased ascorbic acid levels[7,8]. The principal diagnostic feature of diabetes mellitus is elevated blood glucose level, which leads to increased formation and accumulation of advanced glycation products (AGEs) and sorbitol concentration, which play an important role in diabetic complications, such as retinopathy, neuropathy, and renal dysfunction[9].

Knowledge about diabetes mellitus existed in ancient Egypt and Greece. The word "diabetes" is derived from the Greek word "Diab" (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); "mellitus" is the Latin word for "sweetened with honey" (refers to the presence of sugar in the urine)[2]. According to ancient Hindu physicians, "Madhumeha" is a disease in which a patient passes sweet urine and exhibits sweetness all

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Foundation Project: This work was funded by University Grants Commission, New Delhi.

over the body, such as in sweat, mucus, breath, and blood. It was recommended that the low carbohydrate diet and almost total withdrawal of animal fats should be taken by the patients suffering from Madhumeha, whereas obese adults should live on low calorie diet. There are two types of Diabetes mellitus: Type 1, "Juvenile diabetes mellitus" (Insulin dependent diabetes mellitus), which is hereditary and is treated by insulin, and Type 2, "Adult type" (Non-insulin dependent diabetes mellitus), which occurs in elderly people and is treated by controlling the diet and oral hypoglycemic drugs[2]. The drugs which lower the blood sugar level or treat the symptoms of diabetes mellitus are known as hypoglycemic drugs. It can be categorized into insulin and insulin preparation, which are employed only parenterally, and oral hypoglycemic drug which can be administered orally[2].

Plants have always been a good source of drugs. The ethnobotanical information reports about 800 plants that may possess anti-diabetic potential[4,10]. The beneficial uses of medicinal plants in traditional system of medicine of many cultures are extensively documented. Several plants have been used as dietary adjuvant and in treating the number of diseases even without any knowledge on their proper functions and constituents. This practice may be attributed to the uncompromised cost and side effects of synthetic hypoglycemic agents[5]. Although numerous synthetic drugs were developed for the treatment of diabetes mellitus but the safe and effective treatment paradigm is yet to be achieved. Medicinal foods are prescribed widely even when their biologically active compounds are unknown, because of their safety, effectiveness, and availability[6]. In India, indigenous remedies have been used for the treatment of diabetes mellitus since the time of Charaka and Sushruta[4]. The World Health Organization (WHO) has recommended the evaluation of traditional plant treatments for diabetes as they are effective, non-toxic, with less or no side effects and are considered to be excellent candidates for oral therapy[11]. Animal models of diabetes are of great importance in understanding the pathophysiology and deciding treatment strategy of diabetes. Diabetes mellitus can be induced by pharmacological, surgical or genetic manipulations in several animal species. Most experiments in diabetes are carried out on rodents, although some studies are still performed in larger animals[12]. The aim of the present review is to focus on the role of traditional therapeutics and natural medicines from traditional medicinal system for the treatment of diabetes mellitus. The hypoglycemic effect of several plants used as anti-diabetic remedies has been confirmed, and the mechanisms of hypoglycemic activity of these plants are still in progress. New natural products reported from 2009 to 2011 with anti-diabetic potential tested in the streptozotocine induced diabetic rats, which have potent medicinal activities with diverse structures, have been reviewed here.

2. Mechanism of action of anti-diabetic drug

The aim of the treatment of diabetes is to reduce the blood glucose level. Anti-diabetic drug can act in different ways such as stimulation of beta-cell of pancreatic islet to release insulin, to resist the hormones which rise blood glucose, icrease the number and sensitivity of insulin receptors, increase the glycogen content, enhance the use of organ glucose in the tissue, free radicals scavenging, resist lipid peroxidation, correct the metabolic disorder of lipid and protein and promote microcirculation in the body[13]. Free radicals damage cellular molecules, DNA, proteins and lipids leading to altered cellular functions and antioxidants level[14]. Proteins such as elastin, laminin, and collagen are the major targets of free radicals in the diabetic patients. Due to high level of sugar in the body, these proteins are modified and converted to glycoproteins. Modifications of proteins present in lens, vascular wall and basement membranes are associated with the development of diabetes complications such as cataracts, microangiopathy, atherosclerosis and nephropathy. In diabetes mellitus, there are also multiple abnormalities in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). Lipid peroxidation and AGEs are formed by non-enzymatic glycosylation of proteins. AGEs tend to accumulate in tissues and cause abnormalities in cell and tissue functions. In addition, AGEs also bind to specific macrophage receptors and change vascular permeability. In nucleic acids and histones, AGEs cause mutations and altere gene expression[15]. There are different classes of anti-diabetic drugs available in the market which exert their effect in different ways. e.g., sulfonylureas and meglitinides stimulate beta cells in the pancreas to produce more insulin, thiazolidinediones increase the sensitivity of muscles and other tissues to insulin, biguanides decrease gluconeogenesis in the liver and alpha-glucosidase inhibitors delay the absorption of carbohydrates from the gastrointestinal tract[16]. During the normal digestion process, the body turns the carbohydrate into glucose which is utilised by the tissue in the presence of insulin. However, in diabetic, due to inadequate insulin secretion and action, glucose accumulates in the blood and causes secondary complication[2].

There are various types of phytoconstituent present in the plant material belonging to different chemical classes. Phytoconstituents like alkaloids inhibit alpha-glucosidase and decrease glucose transport through the intestinal epithelium. Imidazoline compounds stimulate insulin secretion in a glucose-dependent manner. Polysaccharides increase the level of serum insulin, reduce the blood glucose level and enhance tolerance to glucose. Flavonoids suppress the glucose level, reduce plasma cholesterol and triglycerides significantly and increase hepatic glucokinase activity probably by enhancing the insulin release from pancreatic islets. Dietary fibers effectively adsorbes glucose, retard glucose diffusion and inhibit the activity of alpha-amylase and may be responsible for decreasing the rate of glucose absorption and concentration of postprandial serum glucose. Saponin stimulates the release of insulin and blocks the formation of glucose in the bloodstream and ferulic acid stimulate insulin secretion[17].

3. Oral hypoglycemice agents for treatment of diabetes mellitus

Non-insulin dependent diabetes mellitus is becoming a major health problem in developing countries due to modernization of lifestyle. If diet and exercise does not work properly, then oral anti-diabetic medication should be prescribed to the patients. Based on the mechanism, anti-diabetic drug can be mainly divided into insulin, insulin-secretagogues, insulin sensitivity improvement factor, insulin-like growth factor, aldose reductase inhibitor, alpha-glucosidase inhibitors and protein glycation inhibitor[13]. Insulin and various oral anti-diabetic agents such as sulfonylureas, biguanides, alpha-glucosidase inhibitors, and glinides are the olny option available for the management of diabetes mellitus. They can be used in the form of monotherapy or in combination with other drugs to get better results. In some cases of diabetes, aldose reductase inhibitor has also been used. Sulfonylureas, biguanide, alpha glucosidase inhibitors, aldose reductase inhibitor, thiazolidinediones, carbamoylmethyl benzoic acid, insulin-like growth factor are the main class of the available anti-diabetic drug[13]. Medicinal plants, since immemorial times, have been used in virtually all cultures as a source of medicine. However, the hypoglycemic effects of some herbal extracts have been confirmed in human and animal models of type 2 diabetes. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officianalis* and used to treat diabetes. Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from a herb[16].

4. Herbal remedies for treatment of diabetes mellitus

Plants are used by people since very early time for food, cloths and eventhough as a source of medicine. Plants derived products have been popular all over the world for the centuries. Some herbs have beta-cells regeneration stimulating power. In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity, cholesterol-lowering action and restore the liver glycogen level. Tribal and other people of different countries used different type of plants for the treatment of diabetes[16]. The ethnobotanical information reports about 800 plants that may possess anti-diabetic potential and more than 1200 species of plants have been screened for activity on the basis of ethnopharmacology or on random basis. Herbal anti-diabetic drug mainly belongs to plant, marine algae and fungi to phytogenetically advanced classes of compounds[2]. Medicinal plants that are the most effective and the most commonly studied in relation to diabetes and its complications are *Gentiana olivieri*, *Bauhinia forficata*, *Eugenia jambolana*, *Lactuca indica*, *Mucuna pruriens*, *Tinospora cordifolia*, *Momordica charantia*, *Aporosa lindleyana*, *Myrtus communis* and *Terminalia pallida*. These plant materials show varying range of anti-diabetic activity. Among these medicinal herbs, *Momordica charantia*, *Pterocarpus marsupium*, *Trigonella foenum greacum* have been reported to be beneficial in the treatment of type 2 diabetes[10]. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, cartenoids, *etc*., which are frequently implicated for having anti-diabetic effect[18]. Though natural polymers like guar gum, gumacacia and gum arabic have ability to reduce the calorific value of consumed diet by reducing absorption of carbohydrates from the gastrointestinal tract yet in modern allopathic medicine, they were found to have limited use[3].

5. Pharmacologically tested anti-diabetic plant materials in steptozotocin induced diabetic animal model

5.1. Afzelia africana (Fabaceae)

The aqueous extract of stem bark of *Afzelia africana* in diabetic rats at 100 or 200 mg/kg, p.o. dose level for 10 days treatment, significantly reduced the blood glucose levels while the best result was obtained at 200 mg/kg, p.o., signifying its antidiabetic potential[19].

5.2. Allium cepa (Liliaceae)

The essential oil of *Allium cepa* in diabetic rats at 100 mg/kg, p.o. for 21 days treatment, significantly decreased the serum lipids, lipid peroxide formation, blood glucose and increased serum insulin level. From the obtained result, it was found that the mode of action of *Allium cepa* as anti-diabetic may be due to the antioxidant properties of its essential oil components, which signified its anti-diabetic and antihyperlipidaemic activity[20].

5.3. Amaranthus caudatus (Amaranthaceae)

The methanol extracts of leaves of *Amaranthus caudatus* in diabetic rats at a dose of 200 and 400 mg/kg p.o. for 21 d significantly decreased the blood glucose, total cholesterol (TC), triglyceride (TG), LDL and VLDL, but increased HDL level, signifying its antidiabetic activity. Further similar effect was also observed in *Amaranthus spinosus* and *Amaranthus viridis* methanolic extract in the diabetic rats[21].

5.4. Andrographis lineata (Acanthaceae)

The methanol and aqueous extracts of *Andrographis lineata* in diabetic rats at 400 mg/kg, p.o. for 15 days treatment, significantly reduced blood glucose, TC, LDL, VLDL level and an increase in HDL compared to the control group which signified its anti-diabetic and antihyperlipidaemic activity[22].

5.5. Annona squamosa (Annonaceae)

The ethanolic extract of *Annona squamosa* leaves in diabetic rats at 100 mg/kg, p.o. for 30 days treatment,

significantly reduced the levels of blood glucose, glycosylated hemoglobin, urea and creatinine. The efficacy of the *Annona squamosa* extract was comparable with gliclazide and the results showed that this plant has a significant anti-diabetic potential[23].

5.6. Artocarpus heterophyllus (Moraceae)

The ethanol extracts of *Artocarpus heterophyllus* in diabetic rats at a dose level of 400 mg/kg p. o. significantly reduced the blood glucose level, which revealed that the *Artocarpus heterophyllus* extract has significant anti-hyperglycaemic activity[24].

5.7. Asystasia gangetica (Acanthaceae)

The effect of ethanolic extract of *Asystasia gangetica* in diabetic rats at dose levels of 100 and 200 mg/kg, p.o. for 28 days treatment, significantly decreased blood glucose, glycosylated haemoglobin (HbA1C), TC, TG, LDL, VLDL, elevated haemoglobin and HDL levels. Further it increases the levels of superoxide dismutase (SOD), catalase (CAT), reduces glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase (G-6-PDH) and decreases lipid peroxidation (thiobarbituric acid reactive substances). From the obtained result, it was found that *Asystasia gangetica* had significant anti-diabetic and antioxidant activity[25].

5.8. Boerhaavia diffusa (Nyctaginaceae)

The anti-diabetic activity of ethanolic root extract of *Boerhaavia diffusa* in diabetic rats at 100 and 200 mg/kg, p.o. dose level for 15 days treatment, significantly reduced the blood glucose, TG, LDL, TC level but increased HDL and serum transaminase such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and serum alkaline phosphatase (SALP) activity which signified its anti-diabetic potential[26].

5.9. Berberis vulgaris (Berberidaceae)

The saponins and aqueous extract of *Berberis vulgaris* at 62.5 and 25.0 mg/kg, p.o. respectively in diabetic rats for 21 days significantly decreased the blood glucose level. Both extract also restored other indicators, signifying its antidiabetic activity[27].

5.10. Brassica juncea (Brassicaceae)

The aqueous extract of *Brassica juncea* seeds in diabetic rats at a dose of 250, 350 and 450 mg/kg p.o. significantly reduced the blood glucose level. Further its showed insulinomimetic activity in the tested group, signifying its antidiabetic potential[28].

5.11. Caesalpinia bonduc (Fabaceae)

The hydro-methanolic extract of seed of *Caesalpinia bonduc* in diabetic rats significantly reduced the blood glucose level. Further, it also restored the different enzyme levels in the treated group. Thus, the present study reaveld that *Caesalpinia bonduc* have a significant anti-diabetic potential[29].

5.12. Caesalpinia digyna (Caesalpiniaceae)

The anti-diabetic activity of methanolic extract of *Caesalpinia digyna* in diabetic rats at 250 and 500 mg/kg, p.o. for 15 days treatment, significantly reduces blool glucose, TC, LDL and TG but increased HDL level. From these data, we can conclude that methanolic extract of *Caesalpinia digyna* has significant anti-diabetic and hypolipidemic potentials[30].

5.13. Cassia auriculata (Leguminosae)

The aqueous leaf extract of *Cassia auriculata* in diabetic rats at 400 mg/kg, p.o. for 15 days treatment, significantly reduced the fasting blood glucose, plasma insulin, hepatic hexokinase and phosphofructokinase and C-peptide level. Further, it increased the number of islets and beta cells significantly but suppressed glucose-6-phosphatase and fructose-1,6-bisphosphatase activity. From the obtained result, it was found that the plants have anti-diabetic activity which probably due to pancreatic as well as extrapancreatic action[31].

5.14. Cassia glauca (Caesalpiniaceae)

The different solvent extracts of *Cassia glauca* in diabetic rats at 100 mg/kg p.o. were investigated. The acetone extract of *Cassia glauca* was found to lower the serum glucose level significantly compared to the other fraction. From the result, it was found that acetone fractions had significant anti-diabetic activity[32]. In another study, the aqueous extract of leaves and bark of *Cassia glauca* in diabetic rats at 500 mg/kg, p.o. for 21 days treatment, significantly increased the liver glycogen, serum insulin, and HDL level and decreased the fasting blood glucose, glycosylated haemoglobin, TC, and serum TG. From the result, it was found that *Cassia glauca* extract had significant anti-diabetic and hypolipidemic activity[33].

5.15. Cassia siamea (Fabaceae)

The methanolic extract of *Cassia siamea* leaves in diabetic rats at 250 and 500 mg/kg for 3 weeks significantly decreased the blood glucose, TC, TG level but increased the HDL level, signifying its antidiabetic potential[34].

5.16. Cinnamomum zeylanicum (Lauraceae)

The aqueous extract of *Cinnamomum zeylanicum* in diabetic rats at a dose of 30 mg/kg, p.o. for 21 days treatment, significantly reduced the hyperglycemia and nephropathy. Further, it has upregulation of uncoupling protein-1 and glucose transporter 4 in the brown adipose tissues and muscles, which signified its anti-diabetic potential[35].

5.17. Cleome aspera (Capparaceae)

The methanolic extract of whole plant of *Cleome aspera* in diabetic rats at a dose level of 400 mg/kg, p.o. significantly reduced the blood glucose levels, which signified its anti-diabetic potential[36].

5.18. Clitoria ternatea (Fabaceae)

The aqueous extract of Sankhu pushpam (*Clitoria ternatea*) in diabetic rats at 100 mg/kg, p.o. for 14 days treatment significantly reduced the blood glucose level, which signified its anti-diabetic potential[37].

5.19. Coccinia indica (Cucurbitaceae)

The hydro-alcoholic chronic administration of *Coccinia indica* fruit extracts in diabetic rats at 200 mg/kg, p.o. for 14 days treatment, significantly reduced the blood glucose level, which signified its anti-diabetic potential. Further effect was compared with the standard anti-diabetic drug glibenclamide[38].

5.20. Cucumis sativus (Cucurbitaceae)

The ethanol extracts of fruit of *Cucumis sativus* in diabetic rats at 200 and 400 mg/kg p.o. significantly lowered the elevated blood glucose, cholesterol and LDL level, which signified its anti-diabetic potential. Further 400 mg/kg p.o. was found to be more significant compare to other tested dose[39].

5.21. Decalepis root (Asclepiadaceae)

The *Decalepis* root extract in the diabetic rats significantly reduced the blood glucose level. Further it also restored the antioxidant level in the body, signified its anti-diabetic and antioxidant activity[40].

5.22. Diospyros peregrina (Ebenaceae)

The methanol extract of *Diospyros peregrina* in diabetic rats at 150 and 300 mg/kg p.o. significantly decreased the blood glucose level whereas activities of SOD, CAT, and GSH were found to be increased in a dose dependent manner, signified its anti-diabetic potential. Further 300 mg/kg p.o. was found to be more effective compared to other tested dose and almost comparable to that of standard glibenclamide[41]. In another study, the extract of *Diospyros peregrina* in diabetic rats at the dose levels of 50 and 100 mg/kg, p.o. for 28 days treatment, significantly decreased the blood glucose level in a dose dependent manner. Furthe the activities of SOD, CAT, and GSH were found to be increased in extract treated diabetic rats compared to the normal group[6].

5.23. Dodonaea viscosa (Sapindaceae)

The water extract and polar fraction of ethanol extract of *Dodonaea viscosa* in diabetic rats at 400 mg/kg for 15 days treatment, significantly reduced blood glucose level. Further altered levels of lipids, thiobarbituric acid reactive substances (TBARS), and non-enzymatic and enzymatic antioxidants were restored in the extract treated group. From the obtained result, it was found that *Dodonaea viscosa* had a significant anti-diabetic potential[42].

5.24. Enicostemma littorale (Gentianaceae)

The aqueous extract of *Enicostemma littorale* in diabetic rats at 1 g/kg, p.o. for 3 weeks significantly decreased the blood glucose, serum urea and creatinine level. Further histology of glomerular function suggested its nephroprotective activity[43].

5.25. Eucalyptus globules (Myrtaceae)

The alcoholic extract of *Eucalyptus globules* in diabetic rats at 0.05, 0.10, 0.20 and 0.40 g/kg, p.o for 21 days treatment, significantly decreased the serum glucose levels. Further it increased serum insulin level in a dose dependent manner, which signified its anti-diabetic activity[44].

5.26. Holarrhena antidysenterica (Apocynaceae)

The methanolic extract of *Holarrhena antidysenterica* seeds in diabetic rats at 250 mg/kg, p.o. for 18 days treatment, significantly decreased the blood glucose, TC, TG levels and increased liver glycogen, which signified its anti-diabetic potential[45].

5.27. Hybanthus enneaspermus (Violaceae)

The alcoholic extract of *Hybanthus enneaspermus* in diabetic rats at a dose of 125, 250 and 500 mg/kg p.o. for 21 d significantly decreased the blood glucose level, which signified its antidiabetic potential[1].

5.28. Hypericum perforatum (Hypericaceae)

The ethyl acetate extract of *Hypericum perforatum* in diabetic rats at 50, 100 and 200 mg/kg doses for 15 d significantly decreased the blood glucose, TC, TG, glucose-6-phosphatase levels. Further it increased the tissue glycogen content, HDL and G-6-PDH, which signified its antidiabeti activity[46].

5.29. Lawsonia inermis (Lythraceae)

The ethanolic extract of *Lawsonia inermis* in diabetic rats at 150, 300 and 500 mg/kg, p.o. dose level for 28 days treatment, significantly decreased the blood glucose level and increased body weight, which signified its anti-diabetic potential[47].

5.30. Leonotis leonurus (Lamiaceae)

The aqueous extract of *Leonotis leonurus* leaves in

diabetic rats at 125, 250 and 500 mg/kg, p.o. for 15 days treatment, significantly reduced the blood glucose and LDL but increased HDL level, which signified its anti-diabetic potential[48].

5.31. Litsea coreana (Lauraceae)

The total flavonoids of *Litsea coreana* leves in diabetic rats at 400 mg/kg, p.o. for 6 weeks, significantly increased insulin sensitivity, serum HDL cholesterol level and SOD activities. Further it decreased body weight, serum free fatty acids, TC, TG, LDL cholesterol, C-reactive protein and malondialdehyde content. It also attenuated pathologic alterations in liver and pancreatic islet. These results suggested that total flavonoids of *Litsea coreana* could ameliorate hyperglycemia, hyperlipoidemia, inflammation and oxidation stress, as well as insulin resistance of type 2 diabetes[49].

5.32. Madhuca longifolia (Sapotaceae)

The methanolic extract of *Madhuca longifolia* bark in diabetic rats at 100 and 200 mg/kg, p.o. dose level for 21 days treatment, significantly reduced the blood glucose level in a dose depebdant manner, which signified its anti-diabetic activity[50].

5.33. Morus rubra (Moraceae)

The aqueous leaf extract of *Morus rubra* in diabetic rats at 100, 200 and 400 mg/kg, p.o. for 21 days treatment, showed a dose-dependent reduction of fasting blood glucose. Further 400 mg/kg (p.o.) treated group showed significant reduction in glycosylated haemoglobin with a concomitant elevation in plasma insulin and C-peptide levels. However, the altered serum lipids in the treated group were also restored significantly. The activity of antioxidant enzymes and content of reduced glutathione in erythrocytes and in liver were found to be significantly increased, while serum and hepatic lipid peroxides were suppressed. The results revealed that it had significant anti-diabetic and antioxidant activity[51].

5.34. Nyctanthes arbor-tristis (Oleaceae)

The ethanol extract of Nyctanthes arbor-tristis in diabetic rats at the dose levels of 250 and 500 mg/kg, p.o. dose level, significantly reduced the blood glucose level in a dose-dependent manner which signified its anti-diabetic activity[52].

5.35. Olea europaea (Oleaceae)

The alcohol extract of *Olea europaea* leaves in diabetic rats at 0.10, 0.25 and 0.50 g/kg, p.o. dose level for 14 days treatment, significantly decreased the serum glucose, TC, TG, urea, uric acid, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) while it increased the serum insulin level. From the result, it was found that the anti-diabetic effect of the extract was more effective than the standard glibenclamide[53].

5.36. Otostegia persica (Lamiaceae)

The alcoholic extract of *Otostegia persica* in diabetic rats at 200, 350 and 500 mg/kg, p.o. dose level for 3 weeks, significantly decreased the blood glucose level, which signified its anti-diabetic potetial[54].

5.37. Phlomis persica (Lamiaceae)

The methanol extract of the aerial parts of *Phlomis persica* in diabetic rats at dose levels of 100 and 200 mg/kg, p.o. for 10 days treatment, significantly reduced the fasting blood glucose and increased serum insulin levels. Furthermore, hepatic transporter associated protein (TAP), SOD, CAT, and GPx increased and TBARS decreased in the treated group. The result showed that it had anti-diabetic and antioxidant activity[55].

5.38. Punica granatum (Lythraceae)

The hydro-alcoholic extract of *Punica granatum* peels in diabetic rats at a dose of 400 mg/kg, p.o. dose level for 2 weeks, significantly decreased the plasma glucose and lipid indicator, which signified its anti-diabetic potential[56].

5.39. Rhus coriaria (Anacardiaceae)

The ethanolic extract of *Rhus coriaria* in diabetic rat at 200 and 400 mg/kg, p.o. dose level for 21 days treatment, showed significant reduction in the blood glucose and LDL level but enhancement of HDL level, which signified its anti-diabetic potential[57].

5.40. Rosa canina (Rosaceae)

The ethanol extract of *Rosa canina* fruits in diabetic rats at 250 mg/kg, p.o. for 7 days treatment, possessed a remarkable hypoglycemic activity. Further, chloroform, ethyl acetate, butanol and aqueous extract of *Rosa canina* were also tested in the diabetic rats and the results showed that aqueous extract possessed significant anti-diabetic activity compared to the other extract[58].

5.41. Salmalia malabarica (Bombacaceae)

The hydro-methanolic (2:3, v/v) extract of the sepals of *Salmalia malabarica* in diabetic rats significantly decreased the blood glucose level. Further it decreased the level of CAT and peroxidase were decreased the levels of conjugated diene and TBARS in a significant manner. Moreover, it also restored the serum SGOT, SGPT and glycated haemoglobin level, which signified its anti-diabetic activity[59].

5.42. Sansevieria roxburghiana (Ruscaceae)

The hydroalcoholic extract of *Sansevieria roxburghiana*

rhizome in diabetic rats at 50 and 100 mg/kg, p.o. for 15 days treatment, significantly reduced the blood glucose level in a dose dependent manner. Further it restored the serum biochemical indicators, decreased lipid peroxidation and recovered GSH and CAT. From the result, it was found that *Sansevieria roxburghiana* had remarkable anti-diabetic activity[60].

5.43. Stachytarpheta indica (Verbenaceace)

The ethanolic extract of *Stachytarpheta indica* in diabetic rats at 300 mg/kg and 600 mg/kg, p.o. for 15 days treatment, significantly rduced the blood glucose level, which signified its anti hyperglycemic potential[61].

5.44. Swietenia macrophylla (Meliaceae)

The methanolic extract of the seeds of *Swietenia macrophylla* in diabetic rats at of 200 and 300 mg/kg, p.o. for 12 days treatment, significantly reduced the blood glucose, TC, TG level and elevation of liver glycogen level compared to the control group, which signified its anti-diabetic potential[62].

5.45. Symplocos cochinchinensis (Symplocaceae)

The hexane extract of *Symplocos cochinchinensis* leaves in high fat diet-low streptozotocin induced type 2 diabetic rats at 250 and 500 mg/kg, p.o. for 28 days treatment, significantly reduced the plasma insulin, plasma and hepatic TC, TG and free fatty acids and significantly increased liver glycogen, justifying its traditional anti-diabetic usage[63].

5.46. Syzygium cumini (Myrtaceae)

The petroleum ether, chloroform, acetone, methanol, and water extracts of *Syzygium cumini* in diabetic rats at 100 mg/kg, p.o. for 21 days treatment, significantly decreased the fasting blood sugar. Moreover, among all the extracts, methanol extract was found to be most active[64].

5.47. Tapinanthus bangwensis (Loranthaceae)

The aqueous extract of *Tapinanthus bangwensis* in diabetic rats at 500 mg/kg, p.o. for 14 days treatment, significantly reduced the blood glucose levels, which signified its anti-diabetic potential[65].

5.48. Terminalia bellerica (Combretaceae)

The hexane, ethyl acetate and methanol crude extracts of *Terminalia bellerica* fruits in diabetic rats at the dose levels of 200, 300 and 300 mg/kg, p.o. for 60 days treatment, significantly increased the plasma insulin and C-peptide level. Further the plant extracts significantly increased body weight and serum total protein and significantly decreased the serum levels of TC, TG, LDL cholesterol, urea, uric acid and creatinine in diabetic rats. Moreover, among all the tested extracts, methanol crude extracts of *Terminalia bellerica* was found to be most effective[66].

5.49. Terminalia superba (Combretaceae)

The methanol/methylene chloride extract of *Terminalia superba* leaves in diabetic rats at 200, 400 mg/kg p.o for 2 weeks significantly decreased the fasting blood glucose levels and reduced polyphagia, polydipsia and increased body weight in the treated group, which signified its anti-diabetic potential[67].

5.50. Thespesia populnea (Malvaceae)

The ethanolic extract of the plant bark and leaf of *Thespesia populnea* in diabetic rats were evaluated for anti-diabetic activity and the results showed that both the ethanolic extract possesed anti-diabetic effect[68].

5.51. Tinospora cordifolia (Menispermaceae)

The hexane, ethyl acetate and methanol extract of *Tinospora cordifolia* stem in diabetic rats at 250 mg/kg, p.o. for 100 days treatment, significantly reduced the blood glucose level. Moreover, this supplementation significantly decreased the glycosylated hemoglobin level, reduced glucokinase and increased glucose-6-phoaphatase activity. Further, it also increased the insulin and C-peptide level which shows the regeneration of beta-cell power of the tested extract. However, among all the tested extracts, supplementation of methanol extract showed more significant result compared to the others[69].

6. Discussion

Diabetes mellitus is a disorder of carbohyderate, fat and protein metabolism mainly caused due to attenuate production of insulin or its inhibitory action. Before there was no synthetic drugs, natural cure was used and they can still be used today. Diabetes is a metabolic disorder which can be considered as a major cause of high economic loss. Moreover, uncontrolled diabetes leads to many chronic complications such as blindness, heart failure, and renal failure. In order to prevent this alarming health problem, the research and development of new hypoglycaemic and potentially anti-diabetic agents are of great importance.

This review discusses the drugs of plant origin which have shown significant hypoglycemic activity, even in some cases with good potency. There is an increasing demand by patients to use the natural products with anti-diabetic activity[70]. Herbal therapy has been used to treat various types of disease including diabetes all over the world successfully[71-73]. From the scientific research, it was found that several plant species have proven efficacy to reduce the sugar level. By screening of anti-diabetic drugs, a large number of plant materials including phytoconstituents were found to possess potent anti-diabetic activity[16]. In this review, a listing of data on medicinal plants used in the treatment of diabetes has been presented. Table 1 contains

Table 1

Anti-diabetic plants from different countries.

Country	Plant
Africa	*Combretum micranthum, Ficus capensis, Cassia sieberiana, Ocimum sanctum, Anacardium occidentale, Jatropha curcas, Allium sativum, Citrus medica, Moringa oleifera, Catharanthus roseus, Tamarindus indica, Carica papaya, Landolphia dulcis, Mesonerum benthamianum, Ocimum viridae, Psidium guajava and Pterocarpus ericens.*
Canada	*Abies balsamea, Acorus calamus, Aralia racemosa, Arisaema triphyllum, Celastrus scandens, Corylus cornuta, Gaultheria procumbens, Juniperus communis, Kalmia angustifolia, Nuphar variegatum, Picea mariana, Populus balsamifera, Populus tremuloides, Prunus serotina, Quercus alba, Quercus rubra, Sassafras albidum, Sorbus Americana, Taraxacum officinale, Thuja occidentalis and Verbascum thapsus.*
China	*Astragalus membranaceus, Panax ginseng, Polygonatum odoratum, Lycium barbarum, Ophiopogon japocicus, Epimedium sagittatum, Lithospermum erythrorhizon, Rheum palmatum, Hordeum vulgare, Codonopsis pilosula, Momordica charantia, Punica granatum, Dioscorea opposita, Allium cepa, Trigonella foenum graecum, Prunella vulgaris and Ephedra sinica.*
India	*Abroma augusta, Abutilum indicum, Aconitum palmatum, Asparagus racemosus, Berberis aristata, Catharanthus roseus, Costus speciosus, Ficus racemosa, Ipomoea batatus, Momordica chrantia, Syzygium cuminii, Trigonella foenum graecum, Urtica dioica, Zingiber officinale, Allium cepa, Allium sativum, Aloe vera, Cajanus cajan, Gymnema sylvestre, Momordica charantia, Ocimum sanctum, Pterocarpus marsupium and Tinospora cordifolia.*
Israel	*Achillea fragrantissima, Achillea fragrantissima, Allium cepa, Coridothymus capitatus, Pinus halepensis, Salvia fruticosa, Silene aspera and Teucrium polium.*
Jordan	*Allium cepa, Artemisia vulgaris, Aloe vera , Alpinia officinarum, Brassica oleraceae, Cichorium pumilium, Cinnamomum zeylanicum, Hibiscus sabdariffa, Juniperus phoenicea, Pisum sativum, Quercus coccifera, Rheum ribes, Sarcopoterium spinosum, Terminalia chebula, Trigonella foenum graecum, Varthemia iphionoides and Zizyphus spina-christi.*
Mexico	*Abutilon trisulcatum, Agave atrovirens, Allium cepa, Aloe barbadensis, Ananas comosus, Argemone mexicanam, Artemisia absinthium, Bidens leucantha, Carica papaya, Cassia fistula, Catharanthus roseus, Jatropha elbae, Musa sapientum, Piper hispidum, Plumbago scandens, Quassia amara, Quercus acutifolia, Senna multiglandulosa, Tamarindus indica, Trigonella foenum graecum and Zizyphus acuminate.*
Morocco	*Ammi visnaga, Carum carvi, Artemisia absinthium, Lactuca sativa, Tetraclinis articulata, Lavandula dentata, Trigonella foeniculum graecum, Allium sativum, Aloe succotrina, Linum usitatissimum, Eucalyptus globulus, Myrtus communis, Sesamum indicum, Punica granatum, Nigella sativ, Prunus amygdalus, Citrus bigaradia, Peganum harmala and Zygophyllum.*
North American	*Abies balsamea, Aralia nudicaulis, Cornus stolonifera, Juniperus communis, Picea mariana, Prunus serotina, Quercus rubra, Solidago canadensis, Sorbus americana, Taraxacum officinale and Verbascum thapsus.*

Table 2

Plants having anti-diabetic activity according to the part used.

Plant part	Plant name
Seed	*Acacia arabica, Bauhinia rectusa, Bougainvillea spectabilis, Caesalpinia bonducella, Cassia fistula, Centratherum anthelminticum, Cuminum nigrum, Leucaena leucocephala, Lithospermum erythrorhizon, Lupus albus and Mucuna pruriens.*
Roots	*Aconitum carmichaeli, Andrographis paniculata, Caeseria esculanta, Cassia auriculata, Ceiba pentandra, Inula racemoma, Launaea nudicaulis, Morus alba, Nymphaea nouchali, Oryza saliva, Panax ginseng and Panax quinquefolium.*
Stem bark	*Adansonnia digitata, Berberis aristata.*
Leaf	*Adhtoda vasica, Aegle marmelos, Aloe barbadensis, Aloe vera, Azadirachta indica, Capparis sepiaria, Catharanthus roseus, Eucalyptus globules, Galega officinalis, Momordica charantia, Murraya koienigii, Olea europaea, Phyllanthus fraternus, Poterium ancisroides, Prunus persica, Rauwolfia serpentine and Tecoma stans.*
Bulb	*Allium cepa and Allium sativum.*
Whole plant	*Althaea officinalis, Cannabis indica, Clerodendron phlomoides, Cynodon dactylon, Euphorbia prostrate, Fumaria parviflora, Gymnema sylvestre, Hamada salicornica and Lagerstroemic speciosa.*
Bark	*Anacardium occidentale, Ficus bengelensis, Floscopa glomerata and Pongamia pinnata,*
Stem	*Amaranthus spinosus.*
Rhizome	*Anemarrhena asphodeloids and Atractylode japonica.*
Aerial part	*Barleria lupulina, Cryptostegia grandiflora, Ephedra distachya and Lepidium ruderale.*
Fruit	*Bhighia sapida, Cyamposis tetragonolobus and Momordica cochinchinemis.*
Tuber	*Discorea batalas and Dioscorea dumentorum.*
Flower	*Musa paradisiacal.*
Heart-wood	*Pterocarpus marsupium.*

list of anti-diabetic plants according to the origin of the country[16], Table 2 shows the list of plants according to the part used[3], Table 3 shows plant list based on its mode of action[17], Table 4 shows plants according to the chemical classes, and Table 5 shows active phytoconstituents having anti-diabetic potential[10].

There are several plant materials belonging to different families used to treat diabetes, and the families of plants with the most potent hypoglycaemic effects include Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae and Araliaceae[71]. Oral glucose tolerance test, streptozotocin- and alloxan-induced diabetic mouse or rat models, and sometimes hereditary diabetic mice like KK Ay mice which

Table 3
Anti-diabetic plants having different modes of action.

Mode of action	Plant name
Insulino mimetic activity	*Abies pindrow, Acacia arabica, Agrimony eupatoria, Aloe barbadensis, Annona squamosa, Averrhoa bilimbi, Bixa orellana, Boerhaavia diffusa, Camellia sinensis, Capsicum frutescens, Cinnamomum zeylanicum Nees, Clausena anisata, Eucalyptus globulus, Ficus religiosa, Hibiscus rosa sinensis, Helicteres isora, Ipomoea batata, Juniperus communis, Olea europia, Swertia chirayata, Scoparia dulcis, Tinospora crispa, Urtifca dioica, Vinca rosea and Zingiber officinale.*
Blood sugar lowering activity	*Abroma augusta, Achyranthus aspera, Ajauga iva, Gymnema sylvestre, Gentiana olivier, Glycerrhiza glabra, Gynura procumbens, Hovenia dulcis, Lupinus albus, lavandulaefolia, Myrtus communis, Memecylon umbellatum, Momordica cymbalania, Mucuna pruriens, Momordica charantia, Nelumbo nucifera, Ocimum sanctum, Pandanus odorus, Panax ginseng, Punica granatum, Picrorrhiza kurroa, Syzygium cumini, Trigonella foenum, Tribulus terrestris, Tinospora cardifolia, Withania somnifera and Zizyphus sativa.*
Effects on glucose utilization and enzyme system	*Allium cepa, Artemisia pallens, Bixa orellana, Caesalpinia bonducella, Capparis deciduas, Cassia auriculata, Coscinium fenestratum, Morus indica, Murraya koeingii, Phyllanthus amarus, Xanthium strumarium and Viscum album.*
Increase glucose uptake	*Andrographis paniculata, Catharanthus roseus, Cryptolepis sanguinolenta, Eclipta alba, Enicostemma littorale, Gymnema montanum, Salacia oblonga and Salacia reticulata.*
Plant acting upon aldose reductase enzyme	*Spinaceae oleracea, Cuminum cyminum, Foeniculum vulgare, Ocimum sanctum, Piper nigrum, Trigonella foenumgraceum, Citrus lemon, Momordica charantia, Citrus sinensis aurantium, Murraya koenigii, Cinamomum zeylencium, Trachyspermum ammi, Psidium guajava, Marmelos bael, Brassica nigra, Malus pumila, Zingiber officinalis, Allium sepa, Allium sativum, Coriander sativum and Vitis vinifera.*

Table 4
Anti-diabetic plants according to the chemical nature.

Category	Plant
Triterpene	*Morinda citrifolia, Momordica dioica, Momordica balsamina, Cucumis trigonus, Coccinia indica and Citrullus colocynthis.*
Flavonoid	*Aegle marmelos, Carica papaya, Morinda citrifolia and Feronia elephantum.*
Sterol	*Abelmoschus esculentus and Diospyros peregrine.*
Coumarin	*Aegle marmelos.*
Saponins	*Panax ginseng and Artocarpus heterophyllus.*
Phenolic	*Vaccinium angustifolium, Terminalia catappa, Punica granatum, Phyllanthus emblica, Luffa tuberose, Mangifera indica, Helicteres isora and Syzygium jambolanum.*
Polysaccharide	*Artemisia sphaerocephala, Ganoderma lucidum, Grifola frondosa, Tamarindus indica, Physalis alkekengi, Lyophyllum decastes, Lodoicea, sechellarum and Limonia acidissima.*
Alkaloid	*Murraya koenigii and Withania coagulans.*

are a model of type II diabetes with hyperinsulinemia, were used for the screening of anti-diabetic drugs[71,74,75]. Various types of mechanism of actions have been proposed for the anti-diabetic activity of these plant materials. Some are related to synthesis, release, cell regeneration of pancreatic ss cells or the increase in the protective effect against insulinase and the increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may involve improved glucose homeostasis such as increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen or decrease of glycogenolysis acting on enzymes, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates, and reduction of the effect of glutathione[71].

In this review, natural products containing terpenoids, alkaloids, flavonoids, phenolics, and some other categories have shown anti-diabetic potential. Additionally, some flavonoids and polyphenols as well as sugar derivatives are found to be effective against the inhibitory activities of alpha-glucosidase and aldose reductase. Most of the plant extracts exhibiting hypoglycemic, hypolipidemic, and antioxidant effects in animals may be helpful to treat diabetes and associated complications in human[10]. Therefore, much effort should be focused on assessing natural products and herbal plants for the discovery of potentially useful alpha-glucosidase inhibitors and aldose reductase inhibitors or other treatment approaches to diabetes[10]. Out of an estimated 250 000 higher plants, less than 1% have been screened pharmacologically in regard to diabetic mellitus. *Momordica charantia* and *Eugenia jambolana* are very effective in controlling glucose levels in chemically induced mild to severe model of diabetes mellitus in rodents and seem to work by stimulating kinases involved in peripheral utilization of glucose. Although all these plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity, not all were effective in severe experimental diabetes and its related complications[4].

In conclusion, this paper has presented a list of anti-

Table 5
Active phytoconstituents having anti-diabetic potential.

Isolated constituent	Plant name	Family
Casuarine 6-o-a-glucoside	*Syzygium malaccense*	Myrtaceae
Bis-benzylisoquinoline-type alkaloid	*Stephania tetrandra*	Menispermaceae
Isoquinoline alkaloid, schulzeine a, band c	*Penares schulzei*	Calthropellidae
Tecomine, 5b-hydroxyskitanthine and boschniakine	*Tecoma stans*	Bignoniaceae
Pyrrolidine alkaloid, radicamine a and b	*Lobelia chinensis*	Campanulaceae
Quinolizidine alkaloid	*Talinum paniculatum*	Portulacaceae
Polyhydroxylated alkaloid	*Morus alba*	Moraceae
Calystegine	*Nicandra physalodes*	Solanaceae
Isoquinoline alkaloid	*Coptis japonica*	Ranunculaceae
Sugar-mimic alkaloid	*Angylocalyx pynaertii*	Leguminosae
6-hydroxy-flavonoid	*Origanum majorana*	Lamiaceae
Flavonoid compound	*Myrcia multiflora*	Myrtaceae
Isoaffineyin	*Manikara indica*	Sapotaceae
Flavonol glycoside	*Eucommia ulmoides*	Eucommiaceae
Isoorientin	*Cecropia obtusifolia*	Ceropiaceae
Isorhamnetin-3-o-b-d-glucoside	*Salicornia herbacea*	Chenopodiaceae
Kaempferitrin	*Bauhinia forficata*	Leguminosae
Flavonoid glycoside	*Myrcia multiflora*	Myrtaceae
Sesquiterpene lactone	*Lactuca indica*	Compositae
Sesquiterpenoid	*Ferula mongolica*	Umbelliferae
Friedelane-type triterpene	*Salacia chinensis*	Celastraceae
Olean-13-ene-type triterpene	*Centella asiatica*	Apiaceae
Triterpene dehydrotrametenolic acid	*Poria cocos*	Polyporaceae
Corosolic acid	*Lagerstroemiaspeciosa*	Lythraceae
Abietane-type diterpenoid	*Salvia miltiorrhiza*	Labiatae
Senticoside a	*Acanthopanax senticosus*	Araliaceae
Stevioside	*Stevia rebaudiana*	Asteraceae
Ellagic acid and its derivatives	*Myrciaria dubia*	Myrtaceae
Desmethylyangonine derivatives	*Acosmium panamense*	Fabaceae
Phenolic	*Cuscuta reflexa*	Convovulaceae
	Hyssopus officinalis	Lamiaceae
Magnesium lithospermate b	*Salviae miltiorrhizae*	Labiatae
Allotannin	*Caesalpinia brevifolia*	Fabaceae
Tetra-and penta-o-galloyl-b-dglucose	*Paeonia lactiflora*	Ranunculaceae
Paeoniflorin and 8-debenzoylpaeoniflorin	*Paeonia lactiflora*	Ranunculaceae
Mangiferin-7-o-b-dglucoside	*Anemarrhena asphodeloides*	Liliaceae

diabetic plants used in the treatment of diabetes mellitus. Many new bioactive drugs isolated from plants having hypoglycaemic effects showed anti-diabetic activity equal and sometimes even more potent than known oral hypoglycaemic agents. However, many other active agents obtained from plants have not been well characterized. More investigations must be comducted to evaluate the mechanism of action of medicinal plants with anti-diabetic effect. Consequently, it is necessary to perform toxicological investigation of all plants empirically used in order to avoid the risk of the side effects related to phytotherapy. This review has been presented in a very interactive manner showing geographical region of availability, parts of plant used, mechanism of action and phytoconstituents responsible for particular action; thereby, it will be of great importance to intrested readers to easily identify and go for further research on the plant of their interest.

Acknowledgments

The financial assistance from University Grants Commission, New Delhi, for Dinesh Kumar Patel (Senior Research Fellowship) is greatly acknowledged.

Conflict of interest statement

The authors report no conflict of interest.

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