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## A REVIEW ON: POTENTIAL ANTIDIABETIC HERBAL MEDICINES

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**ABSTRACT:** Diabetes mellitus (DM) is a metabolic disorder of the endocrine system. This frightful disease is found in all parts of the world and is becoming a serious threat to healthcare providers. Nowadays DM is a most spreading disease in the world. In rapidly growing world a number of treatment options are available for treatment of DM. Long term use of allopathic medicinal agents may cause unwanted side effects, resulting uncontrolled blood sugar as well as complications of DM, also DM is highly prone to different types of microorganism and it will affect immune system of body. The use of herbal medicine for the prevention and treatment of DM has been in practice since ancient time. Medicinal plants as a traditional medicine is being used by about 60% of the world's population and India is major contributor to produced herbal medicines. Generally it is believed that the risk associated with herbal medicine is very less, but reports on serious reactions of herbal drugs are also necessary. Numerous herbal plants have been investigated for their potential to treat different types of diabetes. Herbal antidiabetics may delay the development of diabetic complications or correct the metabolic abnormalities. Many of herbal plants and formulations founded effective in treatment of DM. This systemic review paper mainly is focused on herbal plants as antidiabetics in various traditional medicines and explores the herbal plant, isolated active principle and formulation with antidiabetic activity.

**INTRODUCTION:** Diabetes is a chronic metabolic disorder of proteins, fats and carbohydrate, affecting a large number of world population in the world<sup>1</sup>.

Diabetes mellitus is known as a group of chronic metabolic diseases characterized by rise in blood glucose level due to defects in insulin secretion, insulin action, or both. The chronic hyperglycemia in diabetes is associated with long-term damage, dysfunction and failure of various organs especially the heart, eyes, blood vessels, kidneys, and nerves<sup>2</sup>. Various pathological changes are responsible for development of diabetes. Autoimmune destruction of the  $\beta$ -cells of the pancreas causes decrease in insulin secretion and lead to insulin deficiency. The basis of the abnormalities in metabolism of carbohydrate, fat, and protein in diabetes decreases

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insulin on target tissues known as insulin resistance. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Hyperglycemia occurs in patients due to defects in insulin action frequently coexist in the same patient. Impairment of insulin secretion and hyperglycemia characterized by symptom such as polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision.

Impairment of growth and susceptibility to certain infections may also be associated with chronic hyperglycemia. Uncontrolled diabetes characterized with hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome is an acute life-threatening consequence. Long-term complications of diabetes include nephropathy, neuropathy, retinopathy, amputations, foot ulcers, Charcot joints, autonomic neuropathy causing genitourinary, gastrointestinal, and cardiovascular symptoms and sexual dysfunction.

Diabetic subject have an increased incidence of peripheral arterial, atherosclerotic cardiovascular and cerebrovascular disease. Abnormalities of lipoprotein metabolism and hypertension are often found in diabetics<sup>3</sup>.

In past few years, field of herbal medicines are growing exponentially and these drugs are gaining popularity both in world because of it is derived from natural origin and having minimum side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter<sup>4</sup>.

A 60% of world population is using traditional medicines which are derived from medicinal plants.

This review basically focused on Indian herbal drugs and plants used in the treatment of diabetes, especially in India. Diabetes is an important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas.

Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost<sup>5</sup>.

Many of allopathic medicines are available for the treatment of diabetes but somehow they have their own side effect & adverse effect like hypoglycaemia, nausea, vomiting, hyponatremia, flatulence, diarrhoea or constipation, alcohol flush, headache, weight gain, lactic acidosis, pernicious anaemia, dyspepsia, dizziness, joint pain. So instead of allopathic drugs, herbal drugs are a great choice which is having more or less no side effect & adverse effects<sup>6</sup>.

**Epidemiology of diabetes mellitus:** The prevalence of diabetes and pre-diabetes are increasingly high in developing countries, where many of diabetic and pre-diabetic subjects are remained to identify. People with Pre-diabetes often have the chance to reverse both the condition and their chances of going on to develop diabetes by up to 60 % simply through losing even just a moderate amount of weight, adopting a healthy balanced diet and increasing physical activity levels.

According to world health organization (WHO) estimates, in 2005 approximately 1.6 billion adult were overweight and at least 400 million were obese worldwide, number that projected to reach 2.3 billion and 700 million, respectively, by 2015. Paralleling these trends, in 2010 about 300 million people were estimated to have DM globally and this number expected to increase to near about 450 million by 2030<sup>7,8</sup>.

### Types of diabetes

**Type 1 diabetes:** Type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes, may account for five percent to ten percent of all diagnosed cases of diabetes. Risk factors are less well defined for Type 1 diabetes than for Type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes.

**Type 2 diabetes:** Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, which are mainly due to insulin resistance or abnormality in insulin secretion. Type 2 diabetes may account for about 76 - 85 % of all diagnosed cases of diabetes.

Risk factors for Type 2 diabetes include older age, obesity, and family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity.

**Gestational diabetes:** This is glucose intolerance being recognized during pregnancy. It can complicate pregnancy leading to prenatal morbidity and mortality, so clinical detection is important. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20% - 50% of affected women develop type 2 diabetes later in life <sup>9</sup>.

### Other Specific Types of Diabetes:

1. **Genetic defects of the  $\beta$  cell:** These conditions are associated with monogenetic defects in  $\beta$ -cell function. The onset of hyperglycemia is generally before the age of 25 years. They are referred to as maturity-onset diabetes of the young and are characterized by impaired insulin secretion with minimal or no defects in insulin action <sup>30</sup>, these defects are inherited in an autosomal dominant pattern.
2. **Genetic defects in insulin action:** These are abnormalities associated with mutations of the insulin receptor and may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized (development of male sex characteristics in a female) and have enlarged cystic ovaries.
3. **Diseases of the exocrine pancreas:** Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. Also included in this type are cystic fibrosis and hemochromatosis.
4. **Endocrinopathies:** Acromegaly, Cushing's syndrome, glucagonoma, and pheochromocytoma can all cause diabetes.
5. **Drug- or chemical-induced diabetes:** This form of diabetes occurs with drugs or chemicals that affect insulin secretion, increase insulin resistance or permanently damage pancreatic  $\beta$  cells. A commonly encountered example is the

patient taking long-term or high-dose steroid therapy for autoimmune diseases or post-organ transplantation, which can result in steroid-induced diabetes.

6. **Infections:** Viral infections that may cause  $\beta$ -cell destruction include coxsackievirus B, cytomegalovirus, adenovirus, and mumps.

**How do herbal medicines work?** All herbal plants having specific active constituents that gives a therapeutic action. Medicinal plants containing many active chemical constitute, and it is likely that they work together to produce the desired synergetic medicinal effect. The type of environment (climate, bugs, soil quality) in which a plant grew will affect its active components, as will how and when it was harvested and processed that also important for action of herbal medicine.

**How are herbal medicines used?** Herbalists prefer using whole plants rather than extracting single components from them. Whole plant extracts have many ingredients. These active chemical constituents are working together to produce therapeutic effects and also decreases the chances of side effects from any one component. Numbers of herbs are often used together to enhance effectiveness and which is responsible for synergistic actions and to reduce toxicity. Herbalists must take many things into account when prescribing herbs. For example, the genus or species and diversity of the plant, the plant's habitat, how it was stored and processed, and whether or not there are contaminants.

**What is herbal medicine good for?** Herbalists treat many conditions such as diabetes, inflammations, rheumatoid arthritis, cancer, menopausal symptoms, asthma, epilepsy, depression, eczema, parkinsonism, premenstrual syndrome, migraine, chronic fatigue and irritable bowel syndrome. Herbal preparations are best taken under the guidance or supervision of a trained professional. It is necessary to consult your doctor or herbalist before self-treating. Before initiating herbal medication it is essential to observe the monographs on individual herbs for detailed descriptions of uses as well as risks, side effects, and potential interactions which will helpful for better treatment outcome <sup>10</sup>.

**Rationale of alternative remedies:** Blood glucose level of type 2 diabetic patients can be control with medications and/or by adhering to regular exercise program and a dietary plan. Insulin therapy is needed with T1DM and also require for some patients of T2DM while oral hypoglycaemic drugs not able to maintained desired blood glucose<sup>11,12</sup>.

Rapid urbanization leads modification in lifestyle that cause to increase the risk of non-insulin dependent diabetes mellitus in developing countries and is becoming a major health problem of developing countries. Type 2 diabetic patients are usually placed on a restricted diet and are instructed to do regular exercise, the purpose of which primarily is weight control. Oral hypoglycemic agent could be prescribed if diet and exercise fail to control blood glucose at the desired level<sup>13</sup>.

### Mechanism of oral antidiabetic agents

- Stimulation of beta cells in the pancreas to produce more insulin (sulfonylureas and meglitinides)
- Increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones)
- Decreasing gluconeogenesis by the liver (biguanides)
- Delaying the absorption of carbohydrates from the gastrointestinal tract (alpha-glucosidase inhibitors).

The modern medications for diabetes management have their own drawbacks, ranging from the developing of resistance and side effects to lack of receptiveness in large segment of patients population. Sulfonylureas are becoming less effective in 44% of patients after usage for six years. Also, these treatments are associated with side effects or toxic effects (e.g., thiazolidinediones may cause liver toxicity, sulphonylureas may cause heart disease and increase the body weight gain, diarrhea, flatulence, bloating and abdominal discomfort and pain are the major complaints with glucosidase inhibitors)<sup>14, 15, 16</sup>.

According to literature, two by third of medicine prescribed for use in children have not been proven safe or effective for this patient population<sup>16</sup>.

Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently met with the disease<sup>13</sup>. Addition of herbal medicine in prescription can help to reduced blood sugar level with no or lesser side effects with help of decreasing insulin resistance and alternative medicine will be option for the patient who those are not responding to oral hypoglycemic agents.

The limitations of currently-available oral antidiabetic medication either in terms of efficacy/safety coupled with the emergence of the disease into a worldwide epidemic have encouraged a concerted effort to discover newer drugs that can be used to manage type 2 diabetes more efficiently<sup>17</sup>. Also, with increasing incidence of diabetes mellitus in throughout the world and due to adverse effects of allopathic medicinal agents, there is an obvious need for development of indigenous, economical anti-diabetic crude or purified drugs from botanical or natural sources<sup>18, 19</sup>.

**Herbal medicine since ancient time:** In ancient literature more than 800 plant species have been reported to have potent antidiabetic activity<sup>20</sup>. The ancient or Ayurvedic literature survey is demonstrating that the in India diabetes was practically well known and well-conceived since ancient time. The knowledge of the system of diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age<sup>21, 22</sup>.

Ayurvedic antidiabetic medicinal plant increases Rasas (gastric secretions) and improves digestive power, being Laghu, being Ruksha and gets easily digested in the body decrease output of overall body fluids e.g. sweat, urine etc. Food substances, which are 'madhumehaghna' (antidote), are an important essential principle of therapy for the prameha (diabetes) patient.

Food substance which correct the metabolic imbalance by their action e.g. foods exhibiting 'rasa', 'katu', 'laghu', 'medaghna', properties are old cereals, milk, roasted cereals, horsegram, jawar, barley, raw papaya, jamun, mung dal, tur dal, ragi, drumstick leaves, bittergourd, amla, fig, meat of animals that live in dry region, etc. The original diet modification useful in controlling blood sugar to the same extent as insulin and other hypoglycaemic agents do. But it has some other



influences, which may be useful for the management of the disease and its complications<sup>23</sup>. Indian Materia Medica has mentioned many dravyas, which have been reported effective in Madhumeha (diabetes)<sup>24</sup>. Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha,<sup>22</sup> a special food, which used to be offered at the times of yagna organized by Dakshaprajapati<sup>11</sup>. Many other medicinal plants have been reported as antidibetics which are presented in **table 1**.

**Antidiabetic Plants in Clinical trials:** *Allium cepa* L., *Clerodendron phlomoides* Linn., *Casearia esculenta* Roxb., *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm., *Coccinia indica* Wight & Arn., *Enicostemma littorale* Blume., *Momordica charantia* L., *Pterocarpus marsupium* Roxb., *Ficus bengalensis* L., *Syzygium cumini* L., *Cyamopsis tetragonolobus* (L.) Taub., *Cannabis indica* (Lam.) E. Small & Cronq., and *Cephalandra indica* Naud. Many clinical trials have been reported on herbal medicine and they promising and provided evidences for hypoglycaemic effects of them<sup>23,24</sup>.

*Marrubium vulgare* L. and *Cecropia obtusifolia* Bertol. produced beneficial effects on carbohydrate and lipid metabolisms when it was administered as an adjunct on patients with type 2 diabetes and reduced the blood glucose levels<sup>25</sup>. *Asteracantha longifolia* Nees was reported to improve glucose tolerance in healthy human subjects and diabetic patients. Significant reduction in glucose level was observed when *Panax quinquefolius* L was administered 40 min before glucose load in non-diabetic subjects and the same result was seen in diabetic subjects. *Gymnema sylvestre* cause significant reduction in blood glucose, glycosylated haemoglobin and glycosylated b plasma proteins in T2DM subjects. Intake of *Opuntia streptacantha* Lem. by the type II group was followed by a significant reduction in serum glucose and insulin concentration reached up to 40.8 mg/dL and 7.8  $\mu$ U/mL less than basal values at 180 min. Acute hypoglycaemic effect of nopal was observed in T2DM patients but not in healthy control subjects. Human subjects, when treated with a preparation of *Phyllanthus amarus* Shum. & Thon. whole plant for ten days leads reeducation in blood glucose level.

Treatment with *Withania somnifera* Dunal produced hypoglycemic effect that was comparable with hypoglycemic effects of an allopathic oral hypoglycaemic drug<sup>22,11</sup>.

### Antidiabetic phytoconstituents:

**Alkaloids:** Isolated Casuarine 6-O- $\alpha$ -glucoside from *Syzygium malaccense* L.<sup>110</sup>, schulzeines A, B, & C which is isoquinoline alkaloids was isolated from *Penares schulzei* and two new isolated pyrrolidine alkaloids radicamines A and B from *Lobelia chinensis* have been reported as  $\alpha$ -glucosidase inhibitibors<sup>109-111</sup>. Six bis-benzylisoquinoline-type alkaloids, tetrandrine 2'-N-b-oxide, fangchinoline 2'-N-a-oxide, 2'-N-norfangchinoline, and 2'-N-methyltetrandrinium chloride from *Stephania tetrandra* S. shown antidiabetic activity, cycleanine, and stephenanthrine, were compared with those of fangchinoline and tetrandrine in the STZ-diabetic mice.

Fangchinoline, tetrandrine 2'-N-b-oxide significantly decreased the high blood glucose levels in the diabetic mice. Stephenanthrine and cycleanine was not much effective to reduce glycemia<sup>112</sup>. Isoquinoline alkaloids such as berberine sulphate, palatine sulfate, berberine chloride and berberine iodide from *Coptis japonica* have been reported as aldose reductase inhibition activity<sup>113</sup>.

**Flavonoids:** A 6-hydroxy-flavonoids, 6-hydroxy-apigenin-7-O-b-D-glucopyranoside and 6-hydroxyapigenin, from *Origanum majorana* L., leaves have intestinal  $\alpha$ -glucosidase inhibitory activity<sup>114</sup>. The three new flavonoid compounds, myrciacitrin III, IV and V have been isolated from *Myrcia multiflora* DC. (Myrtaceae) and isolated isoaffineyin from *Manikara indica* have aldose reductase inhibitory activity in rats<sup>115</sup>. Isoorientin from *Cecropia obtusifolia* Bertol, and Kaempferol-3, 7-O-(R)- dirhamnoside (kaempferitrin) was isolated from the *n*-butanol fraction of the leaves of *Bauhinia forficata* Link (Leguminosae) led to a significantly reduce blood sugar level in normal and alloxan-induced diabetic rats<sup>116</sup>. Anthocyanins, a significant group of a polyphenols in bilberries and other berries, may also prevent T2DM and obesity.

Anthocyanins from different sources have been shown significant role in glucose metabolism and insulin level/secretion/action and lipid metabolism *in vitro* and *in vivo*. Many *in vitro* studies suggest that the anthocyanins may decrease the intestinal absorption of glucose by retarding the release of glucose during digestion. Recently, the flavonoids isolated from banana flowers have the potential to activate the insulin and it can be an alternative choice for treatment if T2DM patients with insulin resistance. Flavonoids, especially quercetin have been reported to possess antidiabetic activity. Quercetin stimulates release of insulin and enhanced  $\text{Ca}^{2+}$  uptake from isolated islets cell which suggest a role of flavonoids in T2DM<sup>109</sup>.

**Terpenes:** Isolated sesquiterpenoid derivatives from the air-dried roots of *Ferula mongolica* possess glucosidase inhibitory activity. Three novel sesquiterpene lactones, lactucain A, B and C were isolated from *Lactuca indica* L. along with nine known compounds. *Lactucain C* showed moderate hypoglycemic activity against to lower of plasma glucose<sup>117</sup>. The triterpene dehydrotrametenolic acid isolated from *Poria cocos* have been reported as an anti-hyperglycemic effect in an animal model of non-insulin-dependent diabetes mellitus as an insulin sensitizer<sup>118, 119, 120</sup>. The natural sweetener stevioside from plant *Stevia rebaudiana* Bertoni (Asteraceae), has been reported as antidiabetic. Stevioside, stimulate insulin secretion by direct acting on the  $\beta$ -cells of pancreatic islets, it can be consider a future antidiabetic drug for treatment of type 2 diabetes after proper evaluation<sup>121</sup>.

**Different pharmacological action of herbal antidiabetic remedies:** Mechanism of action of herbal antidiabetic is depending on presence of active chemical component in plant material. Different mechanism of action of herbal medicine is given below<sup>11</sup>:

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation<sup>122</sup>
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes<sup>123</sup>
- Prevention of pathological conversion of starch to glucose<sup>124</sup>

- Stimulation of insulin secretion<sup>125</sup>
- Preventing oxidative stress that is possibly involved in pancreatic  $\beta$ -cell dysfunction found in diabetes<sup>126</sup>
- Reduction in insulin resistance<sup>123</sup>
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells<sup>127</sup>
- Inhibition in renal glucose reabsorption<sup>128</sup>
- Regenerating and/or repairing pancreatic beta cells<sup>127</sup>
- Increasing the size and number of cells in the islets of Langerhans<sup>127</sup>
- Protective effect on the destruction of the betacells<sup>129</sup>
- Inhibition of  $\beta$ -galactosidase and  $\alpha$ -glucosidase<sup>130</sup>
- Improvement in digestion along with reduction in blood sugar and urea<sup>131</sup>
- Cortisol lowering activities<sup>132</sup>
- Stimulation of glycogenesis and hepatic glycolysis<sup>133</sup>
  - Inhibition of alpha-amylase<sup>134</sup>

**Antidiabetic herbal product:** Today, more than 600 medicinal plants have been reported to have antidiabetic potential. Many numbers of medicinal plant preparation and different formulations are available for the treatment of diabetes. Some of potential herbal formulation such as Hyponidd tablets, Mersina capsules, DWN-12, Pancreas tonic, Tincture of Panchparna, Pancreas tonic, Glucomap tablets, GlucoCare, Diaveda capsule, Diagon tablets, Glucolev capsule, Madhumeha churna, Glucolib, Glucolev capsule, Sharang Dyab-Tea, Herbal Hills Jambu, Stevia-33, Diab-FIT, Madhumar Capsule, Daya Stone powder, Diabetone Tablet, Kumari-SAAR, Blue berry and Episulin are available in market.

**Table 1: Medicinal plants with antidiabetic activity**

Plant	Part used	Intervention	Experimental model	Study outcome
<i>Acosmium panamense</i> (Fabaceae)	Bark	Butanol & water extracts	Streptozotocin (STZ) induced diabetic rats	Hypoglycemic activity similar to Glibenclamide <sup>26</sup> .
<i>Aegle marmelos</i> (Rutaceae)	Leaves	Methanolic extract	Alloxan induced hyperglycemic rats	Effectively reduced the oxidative stress induced by alloxan and reduced blood sugar <sup>27</sup> .
<i>Allium cepa</i> (Liliaceae)	Callus, seeds, root, leaves	Direct extract	STZ-induced diabetic rats	Antidiabetic activity <sup>28</sup> .
<i>Allium sativum</i> (Liliaceae)	Bulb	Aqueous extract	STZ-induced diabetic rats	Possesses a beneficial potential in reversing proteinuria in addition to reducing blood sugar, cholesterol and triglycerides in diabetic rats <sup>29</sup> .
<i>Aloe vera</i> (Liliaceae)	Leaves	Water extracts	Alloxan induced diabetic rats	Antidiabetic activity <sup>30</sup> .
<i>Andrographis paniculata</i> (Acanthaceae)	Whole plant	Purified ethanolic extract	High-fructose fat induced diabetic rat	Andrographolide from this plant have hypoglycemic and hypolipidemic effects in high-fat-fructose-fed rat <sup>31</sup> .
<i>Amnona squamosa</i> (Amnonaceae)	Leaves	Water extracts	Alloxan & STZ-induced diabetic rats	Plant has both hypoglycaemic and antidiabetic activity. It seems to act by enhancing insulin level from pancreatic islets, increased utilization of glucose in muscle and inhibited the glucose output from liver. It reverses the abnormal lipid profile seen in diabetic animals. Its margin of safety is high. Extract obtained from leaves of <i>A. Squamosa</i> is useful in maintaining healthy blood sugar and cholesterol levels <sup>32</sup> .
<i>Artocarpus heterophyllus</i> (Moraceae)	Leaves	Flavonoid fraction	Alloxan induced diabetic rats	Flavonoid fraction, which produced hypoglycaemic effects in normal and diabetic rats, seems to act like insulin. In diabetic rats, the flavonoids are unlikely to act by stimulating the release of insulin as alloxan-treatment cause permanent destruction of $\beta$ -cells <sup>33</sup> .
<i>Asparagus racemosus</i> (Asparagaceae)	Entire plant	Ethanolic extract	STZ-induced diabetic rats	Significant antidiabetic activity, antihyperlipidemic and antioxidant properties <sup>34</sup> .
<i>Astragalus membranaceus</i> (Fabaceae)	Entire plant	Water decoction	High fat induced type 2 diabetic mouse	Insulin action in insulin resistant lever of mice was restored significantly. Plant enhanced adaptive capacity of the endoplasmic reticulum and promoted insulin signaling by the inhibition of the expression and activity of PTP1B. The anti-obesity effect and hypolipidemic effects of plant were probably due to decreasing the leptin resistance of mice, which would positively couple with the normalization of plasma insulin levels and reduced hyperglycemia <sup>35</sup> .
<i>Averrhoa bilimbi</i> (Oxalidaceae)	Leafs	Ethanolic extract	STZ-induced diabetic rats	Reduced hyperglycemia and hyperlipidemia <sup>36</sup> .



Plant	Part used	Intervention	Experimental model	Study outcome
<i>Azadirachta indica</i> (Meliaceae)	Leaves	Methanol, chloroform, water extract	<i>In vivo</i> diabetic murine model	Regeneration of insulin-producing cells and corresponding increase in the plasma insulin and c-peptide levels with the treatment of chloroform extract of <i>A. Indica</i> <sup>37</sup> .
<i>Bauhinia candicans</i> (Leguminosae)	Leaves	Methanolic extract/butanolic fraction	Experimentally-induced diabetic rabbits	Reduced plasma glucose level in normal and glucose loaded rabbits and increases the peripheral metabolism of glucose <sup>38</sup> .
<i>Bauhinia forficata</i> (Leguminosae)	Leaf	Water decoction	STZ-induced diabetic rats	The improvement in carbohydrate metabolism seen in the rats treated with <i>Bauhinia forficata</i> decoction does not appear to be linked to the inhibition of glycogenolysis or the stimulation of glycogenesis nor does it appear to act in a way similar to insulin or the sulfonylureas, although it may act by the inhibition of neoglycogenesis in a manner similar to that of the biguanides <sup>39</sup> .
<i>Berberis aristata</i> (Berberidaceae)	Stem	Methanolic extract	STZ-induced diabetic rats	Hypoglycemic and hypolipidemic activity <sup>40</sup> .
<i>Beta vulgaris</i> (Chenopodiaceae)	Leaves	Aqueous and methanolic extracts	Alloxan induced diabetic rats	Reduced blood glucose levels 4h after a administration <sup>41</sup> .
<i>Biophytum sensitivum</i> (Oxalidaceae)	Leaves	Water extracts	STZ-nicotinamide-induced diabetic rats	Significantly reduced the blood glucose and glycosylated haemoglobin levels and significantly increased the total haemoglobin, plasma insulin and liver glycogen levels in diabetic rats. It also increased the hexokinase activity and decreased glucose-6-phosphatase, fructose-1, 6-bisphosphatase activities in diabetic rats <sup>42</sup> .
<i>Bixa orellana</i> (Bixaceae)	Seeds	Crude annatto extract	STZ-induced diabetic dogs	Lowered blood glucose by stimulating peripheral utilization of glucose, and it is possible that this glucose-lowering extract might be of pharmacological importance <sup>43</sup> .
<i>Boerhavia diffusa</i> (Nyctaginaceae)	Leaves	Aqueous extract	Alloxan diabetic rats	Oral administration of <i>B. Diffusa</i> leaf extract (blet) at 200 mg/kg of body weight for 4 weeks resulted in significant reduction in serum and tissue cholesterol, free fatty acids, phospholipids, and triglycerides. Moreover, blet supplementation was found to be more effective than glibenclamide in the treatment of diabetic rats <sup>44</sup> .
<i>Brassica nigra</i> (Brassicaceae)	Seeds	Aqueous, ethanol, acetone and chloroform extracts	STZ-induced diabetic rats	Aqueous extract to diabetic animals daily once for one month brought down fasting serum glucose (FSG) levels while in the untreated group FSG remained at a higher value. In the treated animals the increase in glycosylated hemoglobin (HbA1c) and serum lipids was much less when compared with the levels in untreated diabetic controls <sup>45</sup> .
<i>Bryonia alba</i> (Cucurbitaceae)	Root	Alcoholic extract	Alloxan induced diabetic rats	Significant blood glucose reduction <sup>46</sup> .
<i>Caesalpinia bonducella</i> (Caesalpinaceae)	Seeds	Aqueous and ethanolic extracts	Chronic type 2 diabetic rat	Potent hypoglycemic activity in chronic type 2 diabetic rats <sup>47</sup> .
<i>Camellia sinensis</i> (Theaceae)	Leaf	Aqueous extract	Alloxan induced diabetic rats	Hyperglycemic effect that may be caused in part by the reduction of intestinal glucose absorption <sup>48</sup> .



Plant	Part used	Intervention	Experimental model	Study outcome
<i>Eucalyptus globules</i> (Myrtaceae)	Leaves	Aqueous extract	STZ-induced diabetic mice	The antihyperglycemic action of eucalyptus is associated with the stimulation of insulin secretion and enhancement of muscle glucose uptake and metabolism <sup>62</sup> .
<i>Eugenia jambolana</i> (Myrtaceae)	Seeds	Ethanol extract	Alloxan-induced diabetic rats	Hypoglycemic effect <sup>63</sup> .
<i>Ficus hispida</i> (Moraceae)	Bark	Ethanol extract	Alloxan-induced diabetic rats	Increased glycogen synthesis in the liver and muscles and also enhanced uptake of glucose in the peripheral tissues <sup>64</sup> .
<i>Fraxinus excelsior</i> (Oleaceae)	Seeds	Aqueous extract	STZ-induced diabetic rats	Potent hypoglycaemic and anti-hyperglycaemic activities <sup>65</sup> .
<i>Ginkgo biloba</i> (Ginkgoaceae)	Whole plant	Powder	STZ-induced diabetic rats	Possesses antihyperglycemic, antioxidant, and antihyperlipidemia activities in STZ-induced chronic diabetic rats <sup>66</sup> .
<i>Gongronema latifolium</i> Endl. (Apocynaceae)	Leaves	Methanolic extract and different fraction	Alloxan-induced diabetic rats	Preclinical antidiabetic activity supports traditional uses of plant <sup>67</sup> .
<i>Gymnema sylvestre</i> (Asclepiadaceae)	Leaves	Water extracts	Alloxan-induced diabetic rats	Antidiabetic and hypolipidemic activity <sup>68</sup> .
<i>Hibiscus rosa-sinensis</i> (Malvaceae)	Flowers	Ethanol extract	STZ-induced diabetic rats	Hypoglycemic and antihyperglycemic activity <sup>69</sup> .
<i>Ipomoea aquatica</i> (Convolvulaceae)	Leaves	Methanolic extract	STZ-induced diabetic mice	Hypoglycemic and antioxidant activity <sup>70</sup> .
<i>Ipomoea digitata</i> (Convolvulaceae)	Tubers	Hydroalcoholic extract	STZ-induced diabetic rats	Hypoglycemic activity <sup>71</sup> .
<i>Kalopanax pictus</i> (Araliaceae)	Bark	Isolated compounds	STZ-induced diabetic rats	Isolated kalopanaxsaponin A has a potent anti-diabetic activity in contrast to a mild activity of hederagenin. In addition, significant hypolipidemic activities of kalopanaxsaponin A and hederagenin were observed <sup>72</sup> .
<i>Lagerstroemia speciosa</i> (Lythraceae)	Leaves	Water extract	STZ-induced diabetic rats	Prominent hypoglycemic activity on experimental diabetic rats through suppression of gluconeogenesis and stimulation of glucose oxidation using the pentose phosphate pathway <sup>73</sup> .
<i>Mangifera indica</i> (Anacardiaceae)	Leaves	Aqueous Extract & Alcoholic extract	Type 2 diabetic human	Significant hypoglycemic activity in high dose and can be successfully combined with oral hypoglycemic agents in type-2 diabetic patients whose diabetes is not controlled by these agents <sup>74</sup> .
<i>Momordica charantia</i> (Cucurbitaceae)	Seeds, fruits, leaves	Various extract	Type 2 diabetic mice, STZ-induced diabetic rats,	A improves glucose tolerance and suppresses postprandial hyperglycaemia in rats, enhance insulin sensitivity and lipolysis, quite effective in lowering blood sugar levels and islet histopathology also showed improvement <sup>75</sup> .
<i>Morus alba</i> (Moraceae)	Leaves	Methanolic extract	STZ-induced diabetic rats	Antidiabetic activity <sup>76</sup> .
<i>Morus indica</i> (Moraceae)	Leaves	Ethanol extract	Alloxan-induced diabetic rats	Help to improve biochemical parameters and normalize glycaemia in diabetic rat <sup>77</sup> .

Plant	Part used	Intervention	Experimental model	Study outcome
<i>Carum carvi</i> (Apiaceae)	Seeds	Ethanolic extract	STZ-induced diabetic rats	Hypoglycemic activity <sup>49</sup> .
<i>Casearia esculenta</i> (Hippocrateaceae)	Roots	Ethanolic extract	Alloxan induced diabetic rats	Hypoglycemic activity and antihyperglycemic <sup>50</sup> .
<i>Cassia auriculata</i> (Hippocrateaceae)	Leaf	Aqueous extract	STZ-induced diabetic rats	Rise in glycogen content and histopathological examination of pancreatic sections revealed that the increased number of islets and beta-cells and shown insulinogenic action <sup>51</sup> .
<i>Catharanthus roseus</i> (Apocynaceae)	Leaf	Powder suspension	STZ-induced diabetic rats	Antidiabetic and hypolipidemic action <sup>52</sup> .
<i>Citrullus colocynthis</i> (Cucurbitaceae)	Roots	Aqueous extract	Alloxan induced diabetic rats	Aqueous extracts caused reduction in blood sugar level and showed improvement in parameters like body weight, serum creatinine, serum urea and serum protein as well as lipid profile and also restored the serum level of bilirubin total, conjugated bilirubin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP) <sup>53</sup> .
<i>Coccinia indica</i> (Cucurbitaceae)	Leaf	Aqueous extract	Alloxan induced diabetic rats	Hypoglycemic and Hypolipidemic activity <sup>54</sup> .
<i>Coriandrum sativum</i> (Umbelliferae)	Seeds	Ethanolic extract	STZ-induced diabetic rats	Treatment with the coriander seed extract (200 mg/kg) increased significantly the activity of the beta cells in companion with the diabetic control rats. The extract decreased serum glucose in streptozotocin-induced diabetic rats and increased insulin release from the beta cells of the pancreas <sup>55</sup> .
<i>Cuminum nigrum</i> (Apiaceae)	Seeds	Flavonoid contents	Alloxan diabetic rabbits	Flavonoids of <i>C. Nigrum</i> possesses insulin triggering and/or insulin-like properties <sup>56</sup> .
<i>Curcuma longa</i> (Zingiberaceae)	Rhizomes	Ethanolic extract	Genetically diabetic KK-Ay mice	Hypoglycemic effects <sup>57</sup> .
<i>Cyamopsis tetragonoloba</i> (Fabaceae)	Beans	Aqueous extract	Alloxan-induced diabetic rats	Continued administration of the extract at the same dose daily for 10 days produced statistically significant reduction in the blood glucose levels [58].
<i>Dioscorea alata</i> (Dioscoreaceae)	Tubers	Ethanolic extract	Alloxan-induced diabetic rats	Significant antidiabetic activity <sup>59</sup> .
<i>Embliba officinalis</i> (Euphorbiaceae)	Leaves	Methanolic extract	STZ-induced diabetic rats	Effectively normalize the impaired antioxidant status in streptozotocin induced diabetes and extract exerted rapid protective effects against lipid peroxidation by scavenging of free radicals and reducing the risk of diabetic complications <sup>60</sup> .
<i>Enicostemma littorale blume</i> (Gentianeae)	Whole plant	Aqueous extract	Alloxan-induced diabetic rats	Decrease in plasma glucose level was accompanied with decrease in the level of HbA1c and glucose-6-phosphatase activity in liver. The potent antidiabetic properties of <i>E. littorale</i> have been reported <sup>61</sup> .

Plant	Part used	Intervention	Experimental model	Study outcome
<i>Carum carvi</i> (Apiaceae)	Seeds	Ethanol extract	STZ-induced diabetic rats	Hypoglycemic activity <sup>49</sup> .
<i>Casaria esculenta</i> (Hippocrateaceae)	Roots	Ethanol extract	Alloxan induced diabetic rats	Hypoglycemic activity and antihyperglycemic <sup>50</sup> .
<i>Cassia auriculata</i> (Hippocrateaceae)	Leaf	Aqueous extract	STZ-induced diabetic rats	Rise in glycogen content and histopathological examination of pancreatic sections revealed that the increased number of islets and beta-cells and shown insulinogenic action <sup>51</sup> .
<i>Catharanthus roseus</i> (Apocynaceae)	Leaf	Powder suspension	STZ-induced diabetic rats	Antidiabetic and hypolipidemic action <sup>52</sup> .
<i>Citrullus colocynthis</i> (Cucurbitaceae)	Roots	Aqueous extract	Alloxan induced diabetic rats	Aqueous extracts caused reduction in blood sugar level and showed improvement in parameters like body weight, serum creatinine, serum urea and serum protein as well as lipid profile and also restored the serum level of bilirubin total, conjugated bilirubin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP) <sup>53</sup> .
<i>Coccinia indica</i> (Cucurbitaceae)	Leaf	Aqueous extract	Alloxan induced diabetic rats	Hypoglycemic and Hypolipidemic activity <sup>54</sup> .
<i>Coriandrum sativum</i> (Umbelliferae)	Seeds	Ethanol extract	STZ-induced diabetic rats	Treatment with the coriander seed extract (200 mg/kg) increased significantly the activity of the beta cells in comparison with the diabetic control rats. The extract decreased serum glucose in streptozotocin-induced diabetic rats and increased insulin release from the beta cells of the pancreas <sup>55</sup> .
<i>Cuminum nigrum</i> (Apiaceae)	Seeds	Flavonoid contents	Alloxan diabetic rabbits	Flavonoids of <i>C. Nigrum</i> possesses insulin triggering and/or insulin-like properties <sup>56</sup> .
<i>Curcuma longa</i> (Zingiberaceae)	Rhizomes	Ethanol extract	Genetically diabetic KK-Ay mice	Hypoglycemic effects <sup>57</sup> .
<i>Cyamopsis tetragonoloba</i> (Fabaceae)	Beans	Aqueous extract	Alloxan-induced diabetic rats	Continued administration of the extract at the same dose daily for 10 days produced statistically significant reduction in the blood glucose levels [58].
<i>Dioscorea alata</i> (Dioscoreaceae)	Tubers	Ethanol extract	Alloxan-induced diabetic rats	Significant antidiabetic activity <sup>59</sup> .
<i>Emblica officinalis</i> (Euphorbiaceae)	Leaves	Methanolic extract	STZ-induced diabetic rats	Effectively normalize the impaired antioxidant status in streptozotocin induced diabetes and extract exerted rapid protective effects against lipid peroxidation by scavenging of free radicals and reducing the risk of diabetic complications <sup>60</sup> .
<i>Enicostemma littorale blume</i> (Gentianeae)	Whole plant	Aqueous extract	Alloxan-induced diabetic rats	Decrease in plasma glucose level was accompanied with decrease in the level of HbA1c and glucose-6-phosphatase activity in liver. The potent antidiabetic properties of <i>E. littorale</i> have been reported <sup>61</sup> .



Plant	Part used	Intervention	Experimental model	Study outcome
<i>Retama raetam</i> (Fabaceae)	Whole plant	Aqueous extract	STZ-induced diabetic rats	Potent inhibition of renal glucose reabsorption <sup>91</sup> .
<i>Salacia reticulata</i> (Celastraceae)	Leaves	Methanolic extract	STZ-induced diabetic rats	Hypoglycemic and antioxidant activity <sup>92</sup> .
<i>Sclerocarya birea</i> (Anacardiaceae)	Stem bark	Aqueous	STZ-induced diabetic rats	Possesses hypoglycemic activity, and thus lend credence to the suggested folkloric use of the plant in the management and/or control of a adult-onset, type-2 diabetes mellitus in some African communities <sup>93</sup> .
<i>Scoparia dulcis</i> (Plantaginaceae)	Whole plant	Aqueous	STZ-induced diabetic rats	Significant improvement in glucose tolerance in animals, the effect of the extract may have been due to the decreased influx of glucose into the polyol pathway leading to increased activities of antioxidant enzymes and plasma insulin and decreased a ctivity of sorbitol dehydrogenase and extract was effective in attenuating hyperglycemia in rats and their susceptibility to oxygen free radicals <sup>94, 95</sup> .
<i>Silybum marianum</i> (Asteraceae)	Seeds	Silymarin isolated compound	Type 2 diabetic human	Significantly decrease in HbA1c, FBS, total cholesterol, LDL, triglyceride SGOT and SGPT levels in silymarin treated patients compared with placebo as well as with values at the beginning of the study in each group. Silymarin treatment in type II diabetic patients for 4 months has a beneficial effect on improving the glycemic profile <sup>96</sup> .
<i>Salacia Oblonga</i> (Hippocrateaceae)	Root bark	Petroleum ether extract	STZ-induced diabetic rats	Antioxidant and antidiabetic activity <sup>97</sup> .
<i>Spergularia purpurea</i> (Caryophyllaceae)	Whole plant	Water extracts	STZ-induced diabetic rats	Normalized plasma glucose levels a fter two weeks of repeated oral administration <sup>98</sup> .
<i>Suaeda fruticosa</i> (Amaranthaceae)	Arial part	Aqueous extract	STZ-induced diabetic rats	Hypoglycemic effect might be due to an extra-pancreatic action of the aqueous extract <sup>99</sup> .
<i>Sweritia chirata</i> (Gentianaceae)	Leafs	Pet-ether, dichloromethane and methanol fraction	Alloxan-induced diabetic mice	Hypoglycemic activity comparable with glibenclamide <sup>100</sup> .
<i>Syzygium alternifolium</i> (Myrtaceae)	Seeds	Aqueous, ethanolic and hexane fractions	Alloxan-induced diabetic mice	Antihyperglycemic a ctivity <sup>101</sup> .
<i>Tamarindus indica</i> (Fabaceae)	Seeds	Aqueous extract	STZ-induced diabetic rats	Liver glucose-6-phosphatase, liver and kidney glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) activities were restored a fter 14 days treatment <sup>102</sup> .
<i>Telfairia occidentalis</i> (Cucurbitaceae)	Leaves	Ethanolic extract	Alloxan-induced diabetic rat	Reduced blood glucose concentration <sup>103</sup> .
<i>Terminalia chebula</i> (Combretaceae)	Fruits	Ethanolic extract	STZ-induced diabetic rats	Ethanolic extract was more effective than glibenclamide to reduced sugar level <sup>104</sup> .

Plant	Part used	Intervention	Experimental model	Study outcome
<i>Tinospora cardifolia</i> (Menispermaceae.)	Whole plant	Ethanol extract	Alloxan-induced diabetic rats	Antidiabetic activity <sup>105</sup> .
<i>Trigonella foenum-graceum</i> (Fabaceae)	Seeds	Ethanol extract	Alloxan-induced diabetic rats	Antihyperglycemic activity <sup>106</sup> .
<i>Withania somnifera</i> (Solanaceae)	Root/leafs	Flavonoids content	Alloxan-induced diabetic rats	Antihyperglycemic activity and hypolipidemic activity <sup>107</sup> .
<i>Zingiber officinale</i> (Zingiberaceae)	Rhizome	Juice	STZ-induced diabetic rats	Improved oral glucose tolerance, decrease in serum cholesterol, serum triglyceride and blood pressure in diabetic rats <sup>108</sup> .

**Potential future research challenges:** Although many plant species have been validated for their antidiabetic properties and related complications, a need exists for research in the following areas<sup>135</sup>:

- Identify active phytochemical compound(s) directly associated produce hypoglycemia.
- Conduct extensive, large-population clinical studies is required for selected species such as *M. charantia*, *Foenum graecum*, *E. jambo/ana* and *O. tenuiflorum* and many other potential antidiabetics.
- Investigate combination dosages of natural plant product and synthetic drugs to determine the optimal combination for cost-effective therapies.
- Determine the long-term side effects.
- Determine the exact mechanisms behind hypoglycemic and antihyperglycemic activity of the medicinal plant species.
- Assess the inter- and intra-specific variation in secondary metabolite
- Investigate production potential of plant species with clinically proven antidiabetic properties in the USA.
- Develop the potentially easy to consume food products fortified with extracts of plant species with clinically proven hypoglycemic or anti-hyperglycemic properties that can be incorporated into diabetic diets.

**SUMMARY:** Worldwide peoples are successfully using and trusting herbal medicine for the treatment of various health problems. Many of the diabetic patients are getting side effect due to allopathic medication so now patients are relying on alternative therapies with anti-hyperglycemic effects. This comes as no surprise since alternative treatments have been most widely used in chronic diseases, which may be only partially alleviated by conventional treatment. Herbal medications are the most commonly used alternative therapy for lowering blood sugar. However, their safety and efficacy need to be further evaluated by well-designed, controlled clinical studies. However, there are numerous other plants still await scientific inquiry, which have mentioned in the indigenous systems of health care all over the world.

A large number of plants, screened for their antidiabetic effect, have yielded certain interesting leads as mentioned in present article, but till date many plant-based drug is remain to reached such an advanced stage of investigation or development as to substitute or reduce the need for the currently-available oral synthetic drugs. Nevertheless, the interest in herbal drug research continues with an expectation that someday or other, we would be able to bring a safer, efficacious and more effective compound with all the desired parameters of a drug that could replace the synthetic medicines. In recent time interest has been grown toward plant remedies.

Plant has definite promises in the management of diabetes. Isolation and identification of active chemical principle from plant and preparation of standardized dosage can play vital role in management of diabetes.

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