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Review Article

Antidiabetic Activity of Medicinal Plants: An Updated Overview of Streptozotocin and Alloxan-Induced Diabetic Models

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ABSTRACT

Insulin resistance (type 2 diabetes mellitus) leads to the development of hyperglycemia. The present review was aimed at providing an overview of current traditional antidiabetic medicinal plants evaluated by streptozotocin and alloxan. A total of seventy medicinal plants were mentioned with antidiabetic activities in the streptozotocin-induced diabetic model (thirty-six), and alloxan-induced diabetic model (thirty-four). Also, the presence of active ingredients, dose, and significance of antidiabetic action of the medicinal plants were evaluated. In this review, the herbal plants for the treatment of diabetes in the majority of the plants found in Nigeria have been highlighted, and the efficacy of the seventy herbs in the management of diabetes has been evaluated. Diabetes is treated with approximately 40% of medicinal plant leaves. Based on the findings of this review, it is possible to use herbs as adjuvant therapies in the management and treatment of diabetes. Further research into the isolation of phytochemicals and their mechanisms of action will lead to the discovery of newer antidiabetic agents.

Keywords: Alloxan-induced models, Antidiabetic activity, Medicinal plants, Streptozotocin-induced model, Traditional uses.

Introduction

Diabetes mellitus (DM) is an endocrine disorder characterized by hyperglycemia, glycosuria, and hyperlipaemia. It causes serious comorbidities, which are categorized as intense, and subacute. These include, but are not restricted to, retinopathy, neuropathy, nephropathy, heart problems, hypoglycemia, diabetic ketoacidosis, hyperosmolar non-ketotic disorder, polydipsia, frequent urination, absence of energy, visual disability, and weight reduction, and extreme eating (polyphagia).[1,2] The World Health Organization (WHO) supported the evaluation of curative plants based on their effectiveness, low cost, and lack of adverse effects.[3] There are so many antidiabetic plants whose natural products tackle diabetes and directly impact insulin discharge from the pancreas.[4] The International Diabetes Federation estimated that in 2021, diabetes would affect about 783 million people by 2045. Diabetes affects 537 million people, and it is responsible for 6.7 million deaths. In 2021, diabetes claimed the lives of 6.7 million people. Diabetes was predicted to cost the healthcare system at least USD966 billion by 2021, accounting for 9% of total adult expenditure.[5] Animal models for type 1 diabetes range from animals that develop autoimmune diabetes spontaneously to those that undergo chemical ablation of pancreatic beta cells. Obese and non-obese animal models with varying degrees of insulin resistance and beta-cell failure are used to study type 2 diabetes. In recent years, a large number of new genetically modified animals, chemical agents, surgical manipulations, viruses, and diabetogenic hormones have been engineered for the study of diabetes. In contemporary times, the best and quickest way to induce diabetes is with the use of chemicals (alloxan, streptozotocin, dithizone, monosodium glutamate, etc.), viruses, and genetically diabetic rats.

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In recent years, scientists and technologists have worked toward refining techniques that have led to the discovery of chemical agents that physiologically alter the function of the pancreas. The main advantage of using such chemicals is that body changes during and after the induction of diabetes can be observed. The five major diabetogenic agents are chemicals, biological agents, peptides, potentiators, and steroids, but the most common chemical agents are alloxan and streptozotocin.

Streptozotocin (STZ) is a naturally occurring organic substance that produces toxins, resulting in pancreatic beta cells. In synthesis, this is known as 2-deoxy-2- [(methyl radical nitroso amino)-carbonylic] amino. The compound has the atomic formula $C_8H_{15}N_3O_7$ and a general sub-atomic mass of 265.221 g/mol. Figure 1 shows the chemical structure of streptozotocin. Streptozotocin is utilized in clinical exploration to induce hyperglycemia in an animal model.[6] Streptozotocin has also been used in mice to induce Alzheimer's disease by causing memory loss.[7] Streptozotocin prevents DNA synthesis in mammalian and bacterial cells.[8] It triggers a unique reaction with cytosine groups, resulting in DNA degradation and destruction.[9] The STZ enters the pancreatic cells via a glucose transporter, GLUT2, and causes the alkylation of DNA.[10-12]

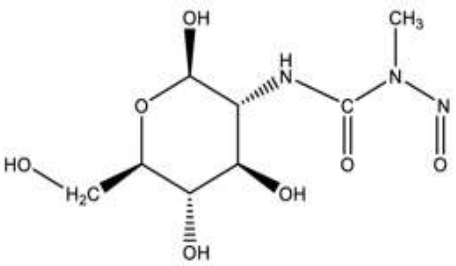

Figure 1: Chemical structure of streptozotocin.

Furthermore, STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release. As a result of STZ action, pancreatic cells are destroyed by necrosis and finally induce insulin-dependent diabetes.[13,14] Streptozotocin is a monofunctional nitrosourea derivative. It is derived from a microbial source, specifically *Streptomyces chromogen*. The compound has been used alone or in combination with other chemotherapeutic agents for the treatment of colorectal carcinomas and other gastrointestinal cancers.

Alloxan is a well-known diabetogenic agent that is frequently used to assess the antidiabetic drug capabilities of natural products and plants derived from diabetes research. It is synthetically recognized as 5,5-dihydroxyl pyrimidine 2,4,6-trione. Alloxan is a natural complex, a urea subsidiary, and a cytotoxic glucose analog.[15] The compound has the subatomic formula $C_4H_2N_2O_4$ and has a virtual subatomic physique of 142.06. The chemical structure of alloxan is represented in Figure 2. Alloxan-induced diabetes is a type of insulin-dependent diabetes mellitus caused by alloxan administration to animals.[16,17] It has been effectively used to induce diabetes in bunnies, mice, rodents, apes, cats, and dogs.[18,19] The mechanism of action generally includes fractional degradation of the beta cells of pancreatic islets.

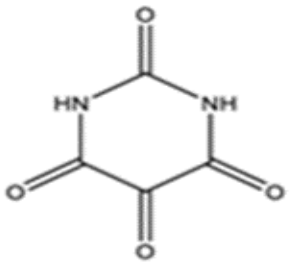

Figure 2: Chemical structure of alloxan.

Methodology

The current review focused on the pharmacological toxicity and safety of streptozotocin- and alloxan-induced models. Scopus, PubMed, EMBASE, and Google Scholar were among the major databases used in the search for relevant data and information. The review was done by selecting seventy research articles published from 2017 to date with STZ or alloxan antidiabetic model.

Results and Discussion

Medicinal plants with streptozotocin-induced antidiabetic activity

Table 1 lists thirty-six medicinal plants that have been reported to have streptozotocin-induced antidiabetic activity. The active ingredients, dosage, and significance of the anti-diabetic action, as well as the experimental model, were examined for each of them. These plant species belong to the family of Rubiaceae (twelve species), Fabaceae (five species), Apocynaceae (four species), Lamiaceae, Leguminosaceae, Asteraceae, and Asclepiadaceae (three species). Also, Loranthaceae, Caesalpiniaceae, and Aloaceae (two species) are included. Anacardiaceae, Conovolulaceae, Caryophyllaceae, Elaeagnaceae, Linderniaceae, Thymelaeaceae, Punicaceae, Portulacaceae, Cucurbitaceae, Capparidaceae, Malvaceae, Celastraceae, Annonaceae, Araliaceae, Moraceae, Mimosaceae, Loganiaceae, Poaceae, Myrsinaceae, Acoraceae, Alangiaceae, Rosaceae, Phyllanthhaceae, Bignoniaceae, Orchidaceae, Liliaceae, Cactaceae, Papilionaceae, Rutaceae, Sterculiaceae, and Basellaceae (one specie) were also documented. To date, the majority of the plants studied have the potential to be used in the traditional management of diabetes.

Antidiabetic activity of medicinal plants in streptozotocin-induced models

Aloe megalacantha Baker

Aloe megalacantha Baker belongs to the family of *Aloaceae*. An ethyl acetate leaf extract of the plant was used in a study to demonstrate its antidiabetic efficacy. Streptozotocin (50 mg/kg) was given intraperitoneally in a single dose. At the dose of 2000 mg/kg bodyweight (BW), there was no toxicity. Based on the toxicity results, 100, 200, and 400 mg/kg BW of plant extracts were administered for 14 days, leading to a significant reduction in fasting blood glucose levels when compared to negative control STZ-induced diabetic mice.[20] Lowering postprandial glucose levels were attributed to *Aloe megalacantha*, due to blockage of glucose absorption, stimulation of peripheral glucose uptake, and reduced glycogenolysis.[21]

Aloe pulcherrima

Aloe pulcherrima belongs to the family of Aloaceae. Leaf latex was used in the experimental procedure to prove the antidiabetic capacity. A solitary portion of streptozotocin (50 mg/kg) was administered intraperitoneally. At the dose of 2000 mg/kg BW of leaf latex, there was no toxicity. Based on the toxicity results, 200, 400, and 600 mg/kg BW, the blood glucose level of diabetic mice significantly decreased in the first 7 days and was observed about 14 days later. It essentially increased diabetic dyslipidemia and bodyweight diabetic mice. [22]

Borreria hispida

Borreaia hispida belongs to the Rubiaceae family. In the experimental procedure to show its antidiabetic effect, methanol and aqueous extracts of the whole plant were utilized. A solitary portion of streptozotocin (60 mg/kg) was administered intraperitoneally. At a dose of 2000 mg/kg BW plant extract, there was no toxicity. Based on the toxicity results, 200 and 400 mg/kg BW of the plant extracts and Glibenclamide at a dose of 600 ug/kg BW, resulted in decreased blood sugar levels, increased high-density lipoproteins, and decreased low-density lipoproteins, triglycerides, and total cholesterol.[23]

Cassia fistula

Cassia fistula belongs to the family of Fabaceae. An ethanolic extract from its pods was utilized to evaluate its antidiabetic action. A solitary portion of streptozotocin (60 mg/kg BW) was administered intraperitoneally. Oral administration of *Cassia fistula* ethanol extract was applied in three doses of 100, 250, and 500 mg/kg BW, as well as Glibenclamide at a dose of 5 mg/kg. When compared to diabetic control rats, there was a significant decrease in blood glucose levels and HbA1c levels, as well as an increase in body weight and hepatic glycogen content after 60 days. At 500 mg/kg BW, the extract enhanced the oral glucose tolerance test. These outcomes were similar to those observed with Glibenclamide.[24] *Cassia fistula* pods contain antioxidants.[25] These are scavenged hyperglycemia-induced free radicals and also have a protective impact on beta cells.

Catharanthus roseus

Catharanthus roseus is a member of the Apocynaceae family. The ethanol leaf extract was employed in an experimental procedure to assess its antidiabetic activity. Streptozotocin was injected intraperitoneally in a single dose of 200–250 mg/kg. At a dose of 1000 mg/kg BW plant extract, there was no toxicity. According to the toxicity results, 1 mg/kg for 60 days of oral administration caused massive lesions in the islets of Langerhans and decreased islet components due to beta-cell damage. The pancreas in streptozotocin- and *Catharanthus roseus*-treated rats showed directed vacuolation and Langerhans of islet cells. The diabetic group had higher blood glucose levels. However, those treated with ethanolic extract had significantly lower blood glucose levels as represented by expanded beta-cells. Meanwhile, streptozotocin and *Catharanthus roseus* were found to lower blood and glucose levels.[26]

Clerodendrum infortunatum

Clerodendrum infortunatum belongs to the family of Lamiaceae. Aqueous extracts from stems and leaves were employed in the experimental procedure to determine its antidiabetic properties. A solitary dose of streptozotocin at 40 mg/kg BW and Glibenclamide dose of 600 g/kg BW at a dose of 2000 mg/kg BW were administered intraperitoneally. There was no evidence of toxicity. According to the toxicity results, 200 and 400 mg/kg oral administration for 40 days resulted in a decrease in glucose levels in *Clerodendrum infortunatum* at the 400 mg/kg BW dose. Even at lower doses of *Clerodendrum infortunatum* (200 mg/kg), the reduction was not statistically significant.[27]

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Drymaria cordata
Drymaria cordata belongs to the family Caryophyllaceae. In testing its antidiabetic characteristics, a methanol leaf extract was used. A dose of streptozotocin at 45 mg/kg BW was administered intraperitoneally. At a dose of 2000 mg/kg BW plant extract, there was no toxicity. Based on the toxicity results, 200 and 400 mg/kg and metformin as control at 150 mg/kg BW were administered orally for 28 days. *Drymaria cordata* had a significant dose-dependent decrease in fasting blood glucose, glycosylated hemoglobin, blood serum lipids, and hepatorenal anti-oxidative. *Drymaria cordata* leaf extract improved oxidative pressure and blood serum lipid levels, supporting the folkloric use of this plant in the treatment of diabetes.[28]

Duvalia corderoyi
Duavalia coderoyi belongs to the family of Apocynaceae. A methanol stem extract was applied when the antidiabetic properties were evaluated. The streptozotocin portion was administered intraperitoneally at a dose of 60 mg/kg and Glibenclamide at a dose of 600 ug/kg. At a dose of 2000 mg/kg BW plant extract, there was no toxicity. Toxicity results showed that 100 and 200 mg/kg BW significantly improved in the treatment group. One month of treatment with *Duvalia corderoyi* caused a decrease in creatinine and urea concentrations. The high concentration (200 mg/kg) of *Duavalia corderoyi* was more effective.[29]

Elaeagnus umbellate
Elaeagnus umbellata belongs to the Elaeagnaceae family. Chloroform and ethyl acetate f extracts have been used to test its antidiabetic activity. A single intraperitoneal infusion of 50 mg/kg BW streptozotocin and an extract from *Elaeagnus umbellata* at a dose of 2000 mg/kg BW were observed not to be toxic to the experimental animals. Based on the toxicity results, 100 and 200 mg/kg and Glibenclamide (0.5 mg/kg BW) were administered orally. These were extremely dynamic against alpha-amylase and alpha-glucosidase. The trichloromethane and acetate D ethyl fraction parts of the extracts were more effective in regulating hyperglycemia in STZ-induced type 2 diabetes in rodents and demonstrated a significant decrease in glucose tolerance.[30]

Lindernia ciliate
Lindernia ciliate belongs to the family of Linderniaceae. The impact of the concentrated methanol extract from the whole plant has been studied. A solitary portion of streptozotocin (45 mg/kg BW) and the extract at a dose of 2000 mg/kg BW showed no toxicity. Based on the toxicity results, 100, 200, and 400 mg/kg BW and a Glibenclamide dose of 10 mg/kg BW were administered intraperitoneally to diabetic rats.

Table 1: Streptozotocin-induced model of some antidiabetic medicinal plants.

SN	Scientific name/ family	Parts used	Extract	Probable mechanism of action	Dose mg/kg	Ref.
1	*Acorus calamus (Acoraceae)*	Rhizomes	Methanol	Reduces the activity of the enzyme's glucose-6 phosphates and fructose-1,6 phosphatase.	200	[40]
2	*Afzelia africana (Fabaceae)*	Stem bark	Aqueous	Insulin potentiation from cells or increased peripheral glucose uptake.	200	[41]
3	*Alangium lamarckii (Alangiaceace)*	Leaves	Alcohol	Improvement in liver glycogen, body weight, and antioxidants.	250, 500	[42]
4.	*Caesalpinia digyna (Caesalpiniaceae)*	Root	Alcoholic	Decreased lipid peroxidase and increased superoxide dismutase and catalyze.	250, 500, 750	[43]
5.	*Chaenomeles sinensis (Rosaceae)*	Fruits	Aqueous ethanol	Blood glucose-lowering effect of extract due to carbohydrate hydrolyzing enzyme inhibition potency.	50, 100	[44]
6.	*Emblica Officinalis (Phyllanthaceae)*	Whole plant	Methanol	Reduced glutathione, glutathione peroxidase, catalase, and decreased lipid peroxidation levels.	100, 200, 300,400	[45]
7.	*Entada phaseoloides (Leguminosae)*	Seed	Ethanol	Protecting pancreas islet cells & stimulating insulin secretion.	25, 50, 100	[46]
8.	*Ficus amplissima (Moraceae)*	Bark	Pet ether	Anti-lipid peroxidative effect.	50, 100, 150	[47]
9.	*Gymnemamontanum (Apocynaceae)*	Stem	Ethanol	An increase in hexokinase, Glucose-6-phosphate dehydrogenase e, and fructose-1,6-bisphosphatase 10 levels was significantly reduced.	25, 50,100, 200	[48]
10.	*Heinsiacrinata (Rubiaceae)*	Leaf	Aqueous	Stimulating the activities of the key glycolytic enzymes towards an increased flux of glucose.	120	[49]
11.	*Ixora pavettain (Rubiaceae)*	Leaves	Ethanol	Increased lipid peroxidation and catalase and decreased antioxidant enzyme.	250, 500	[50]
12.	*Kigelia pinnata (Bignoniaceae)*	Flowers	Methanol	Reduction in total cholesterol and triglycerides showed improvement in lipid profile and body weight.	60	[51]
13.	*Merremia emarginata (Convolvulaceae)*	Whole plant	Methanol	Hexokinase and other metabolizing enzymes enhanced glucose-6-phosphatase and fructose-1-6 diphosphatase.	100, 200, 400	[52]
14.	*Merremia tridentate (Convolvulaceae)*	Root	Aqueous	Anti-lipid peroxidative effect.	50, 100, 150	[53]

15.	*Mulberry (Moraceae)*	Leaves	Methanol ethanol	Improved cellular energy balance by inhibiting NEFA signaling by lowering downstream signaling in the NEFA pathway, as seen by decreased PKC and restored expression of PGC-1, AK2, OXPHOS, and adiponectin.	35	[54]
16.	*Nervilia plicata (Orchidaceae)*	Stem	Alcoholic	Epithelial regeneration, glomeruli expansion, and decrease in serum urea and creatinine levels.	5	[55]
17.	*Ophiopogonis japonicus (Liliaceae)*	Roots	Ethanol	Enhanced GLP-1 level, decreased glucagon level.	225, 450	[56]
18.	*Opuntia dillenii (Cactaceae)*	Whole plant	Ethanol	Increase body weight, reduce fasting blood glucose level, and improve oral glucose tolerance.	100, 200, 400	[57]
19.	*Orthosiphon stamineus (Lamiaceae)*	Leaves	Chloroform	Increases glucose transport across membranes in peripheral tissues, producing an insulin-like impact on glucose consumption. Anti-oxidant potential and enzymes inhibitory Controlled nephropathy	0.5 g, 1 gm	[58]
20.	*Basella rubra (Basellaceae)*	Leaves	Phenolic extract		200, 400	[59]
21.	*Sterculia tragacantha (Sterculiaceae)*	Leaves	Aqueous extract		150, 300	[60]

Administration of the concentrate of three test portions brought about a significant reduction in the levels of serum glucose, total cholesterol, fatty acids, serum glutamic oxaloacetic transaminase, blood serum glutamic pyruvic aminopherase, alanine phosphatase, urea, and creatinine. At 200 mg/kg of plant extract, a significant reduction in plasma glucose levels was contrasted with Glibenclamide.[31]

Plicosepalus acacia

Pilcosepalus acaciae belongs to the family of Loranthaceae. An ethanol extract of the dried flowers has been investigated. *Plicosepalus acaciae* contains flavonoids, glycosides, and phenols. Also, loranthin has been isolated from *Pilcosepalus acaciae*.[32] Catechin, quercetin 3-O-(6-galloyl)-glucopyranoside, glucopyranoside, and catechin 7-O-gallate were all found to be high in antioxidants.[33] A solitary portion of streptozotocin at 35 mg/kg BW was administered intraperitoneally at a dose of 2500 mg/kg BW. There was no evidence of toxicity observed. Based on the toxicity results, 150 and 300 mg/kg BW, as well as metformin at a dose of 150 mg/kg BW, were administered for 15 days. *Plicosepalus acaciae* has a protective reformative effect on pancreatic beta cells. This was attributed to the initiation of beta-prison cell signalling, which leads to improved glucose and lipid uptake.[34]

Phaleria macrocarpa

Phaleria macrocarpa belongs to the family of Thymelaeaceae. The ethanol extract from the fruits has been investigated for antidiabetic capacity. A single infusion of streptozotocin portion at 65 mg/kg BW and the plant extract at a dose of 5000 mg/kg BW showed no toxicity. Based on the toxicity results of 50, 100, and 200 mg/kg, as well as Glibenclamide at 0.5 mg/kg BW, were employed in the experiment. When compared to a diabetic control group, repeated oral administration of an ethanolic extract every day for up to 35 days was shown to be more effective for *Phaleria macrocarpa*, resulting in critical antidiabetic action in STZ-induced diabetic rats. Towards the end of 35 days of treatment, the 200 mg/kg BW ethanol concentrate of *Phaleria macrocarpa* dosage was observed to decrease blood glucose levels.[35]

Punica granatum

Punica granatum belongs to the Punicaceae family. The experimental procedure to demonstrate the antidiabetic potential of the plant involved methanol leaf extract. For 45 days, diabetic rodents received a single dose of STZ at 60 mg/kg BW or the plant extract at a dose of 2000 mg/kg BW intraperitoneal injection. There was no toxicity observed. Based on the toxicity results, 100, 200, 400, and 600 mg/kg BW plant extracts, as well as Glibenclamide at 1 mg/kg BW oral administration in diabetic rats exhibited antidiabetic activities. This was attributed to its cell antioxidant activity, most likely due to the gallic, ellagic acid, and apigenin found in *Punica granatum* methanolic extract.[36]

Portulaca grandiflora

Portulaca grandiflora belongs to the family of Portulacaceae. The ethanolic extract from the aerial parts has been studied for its antidiabetic activity. The experimental animals received a single intraperitoneal injection of streptozotocin at a dose of 50 mg/kg BW. Oral administration of the standard drug metformin at 5 mg/kg BW and the plant extract at a dose of 2000 mg/kg BW for 1-2 days only were observed not to be toxic. Based on the toxicity results, 200 and 400 ug/kg of BW were administered to the animals for 1–21 days. The ethanolic extract of *Portulaca grandiflora* significantly reduced blood glucose levels and improved body weight in the treatment groups.[37]

Trigonella foenum-graecum

Trigonella foenum-graecum belongs to the family of Fabaceae. An aqueous extract from the seeds of the plant has been tested. Experimental animals received a single portion of the streptozotocin dose at 75 mg/kg BW in sterile citrate solution intraperitoneally. The seed extract was administered at a dose of 100 mg/kg. After fenugreek treatment, aspartate transaminase and alanine transaminase levels decreased, while protein levels increased significantly. After each

day's infusions, high-thickness lipoprotein increased, while triglycerides decreased significantly in all groups. Glutathione S-transferase and catalase expanded with treatment, while peroxidase cancer prevention agent compound levels were decreased. Glutathione peroxidase levels increased following infusion.[38] Fenugreek contains 4-hydroxy isoleucine, an amino acid that boosts insulin production while lowering plasma triglycerides and total cholesterol.[39]

Antidiabetic activity of medicinal plants in alloxan-induced models
Reports of antidiabetic activities of 34 medicinal plants in alloxan-induced models are presented in Table 2.

Cassia sophera
Cassia sophera belongs to the Caesalpiniaceae family. The methanolic leaf extract was used to investigate its antidiabetic activity. A dose of 120 mg/kg BW of alloxan was injected intraperitoneally into diabetic rats. At a dose of 2000 mg/kg BW of the plant extract, there was no toxicity. Based on the toxicity results, 50, 100, and 200 mg/kg BW of methanolic extract of *Cassia sophera*, as well as a dose of 5 mg/kg BW of Glibenclamide were administered. For seven days, a significant reduction in fasting blood glucose levels was observed in the oral glucose resistance assessment in the experimental rats. The extract reduced blood glucose levels while significantly improving glucose tolerance and body weight in treated diabetic rats at the end of the fourth, seventh, and fourteenth days.[61]

Caralluma Europa
Caralluma europa belongs to the Asclepiadaceae family. The experimental procedure to test its antidiabetic effect employed the methanol extracts from the aerial parts of the plants. Alloxan monohydrate was freshly prepared in normal saline with a concentration of 1 % at a dose of 200 mg/kg BW.[62] Glibenclamide dose of 20 mg/kg BW and at a plant extract dose of 2000 mg/kg BW were not associated with any observable toxicity. Both extracts have significant antidiabetic activity based on toxicity results of 250 and 500 mg/kg BW. The plant extract contained phenolic compounds such as catechin, quercetin, rutin, ferulic acid, epigallocatechin, and 3,4 dihydroxybenzoic acid, which inhibit lipid peroxidation.[63]

Table 2: Alloxan-induced model of some antidiabetic medicinal plants

SN	Scientific name/ Family	Parts used	Extract	Probable mechanism of action	Dose mg/kg	Ref.
1	*Acanthopanax Senticosus (Araliaceae)*	Whole plant	Aqueous	Potent antioxidant activity leads to antidiabetic activity.	200	[76]
2	*Adina cordifolia (Rubiaceae)*	Leaves	Hydro-alcohol	Increase insulin secretion or prevent glucose absorption in the intestines.	500	[77]
3	*Ajuga Remota (Lamiaceae)*	Leaves	Ethane Aqueous	Percentage reduction in blood glucose levels.	300, 500	[78]
4	*Albizia odoratissima (Mimosaceae)*	Bark	Pet ether $CHCL_3$ methanol	Increased body weight and lower blood glucose levels might be the result of improved glycemic control mechanisms.	250, 500	[79]
5	*Anthocleista djalonensis (Loganiaceae)*	Leaves, stem, bark	Methanol	Alpha-amylase inhibitory mechanism.	1 gm	[80]
6	*Axonopus compressus (Poaceae)*	Leaf	Methanol	Stimulation of the beta cells, Decrease in intestinal absorption of glucose.	250, 500, 1000	[81]
7	*Canthium parviflorum (Rubiaceae)*	Leaves	Methanol	The extract may promote insulin release from pancreatic cells.	200, 300	[82]
8	*Coffea arabica (Rubiaceae)*	Seed	Aqueous	To inhibit glucose-6-phosphatase functioning.	63, 93	[83]
9	*Embelia ribes* (Myrsinaceae)	Berries	Hexane	Following normalization of glycaemic levels in diabetes, body weight increases.	25, 50	[84]
10	*Erythrina Indica (Papilionaceae)*	Stem bark	Alcohol	Dexamethasone-induced increases in blood glucose were inhibited, and glucose tolerance improved.	200, 400	[85]
11	*Fadogia Agrestis Schweinf (Rubiaceae)*	Stem	Aqueous	Hexokinase activity, high-density lipoprotein cholesterol levels, packed cell volume, and hemoglobin levels all decreased significantly.	18,36, 72	[86]
12	*Gymnema sylvestre (Asclepiadaceae)*	Leaves	Ethanol	Increase the utilization of glucose depressing the mobilization of fat.	250, 500	[87]
13	*Hamelia patens (Rubiaceae)*	Stem	Ethanol	Blood glucose, total cholesterol, and triglyceride levels all dropped significantly.	100, 400	[88]
14	*Himalrandia Tetrasperma (Rubiaceae)*	Leaves Bark seeds	Methanol	The mechanism through the decrease the glucose levels.	250	[89]
15	*Loranthus micranthus (Loranthaceae)*	Leaves	Ethanol	Potent immunostimulatory potential effect [91]	250, 400	[90]

16	*Melantha scandens (Asteraceae)*	Leaves	Ethanol	Inhibition of hepatic glucose production.	37, 111	[92]
17	*Pongamia pinnata* (Leguminosae)	Leaf	Pet ether $CHCL_3$ Alcohol	Elevated blood glucose levels.	500	[93]
18	*Rothmannia hispida (Rubiaceae)*	Leaves	Aqueous	Homeostatic mechanism of the body due to insulin.	100	[94]
19	*Senna alata (Fabaceae)*	Leaves	Ethyl acetate fraction	1,3,8- trihydroxy 6-methyl anthraquinone inhibitory agent	2.5	[95]
20	*Gongronema latifoliaum (Apocynaceae)*	Leaves	Aqueous	Reduced inflammatory Increased hepatic protective	6.36 12.72 25.44	[96]

Coccintia grandis
Coccintia grandis belongs to the family of Cucurbitaceae. The ethanolic fruit extract was used to demonstrate its antidiabetic action. A solitary dose of 150 mg/kg BW alloxan prepared in normal saline was infused intraperitoneally to induce diabetes in rats. At a plant extract dose of 2000 mg/kg BW, there was no toxicity recorded. Based on the toxicity results, the toxicity levels of 200 and 400 mg/kg BW were chosen. The rats with plasma glucose levels greater than 300 mg/dl were chosen for the study, which lasted 21 days. In diabetic rats, it was discovered to lower blood sugar levels and prevent weight loss.[64]

Ocimum gratissimum, Vernonia amygdalina, and Moringa oleifera
The antidiabetic activity of *Ocimum gratissimum, Moringa oleifera, and Vernonia amygdalina* tri-herbal formulation of ethanolic extract was investigated. Alloxan was induced by infusing an intraperitoneal dose of 150 mg/kg BW. Various plant extracts at doses of 100, 200, and 400 mg/kg BW were administered orally for 28 days. These tri-herbal extracts showed hypoglycemic and hematological effects.[65]

Galium tricornutum
Galium tricornutum belongs to the family of Rubiaceae. In testing its antidiabetic impact, methanol extracts of the aerial parts of the plant were used. A solitary dose of 150 mg/kg BW alloxan prepared in normal saline was infused intraperitoneally to prompt diabetes in rats. At a dose of 5000 mg/kg BW of the plant extracts, there was no toxicity observed. Based on the toxicity results, 200 and 400 mg/kg BW of methanol extract, and Glibenclamide (5 mg/kg) were investigated. All treatments were observed for 21 days. At 400 mg/kg BW, the plant extract showed a significant anti-hyperglycemic response. It also caused a significant increase in body weight and HDL-cholesterol, as well as a significant decrease in blood serum low-density lipoproteins, fatty substances, and transaminases.[66]

Leucomeris spectabilis
Leucomeris spectabilis belongs to the family of Asteraceae. The experimental rats received a single intraperitoneal infusion of alloxan monohydrate at a dose of 120 mg/kg BW. At the dose of 2000 mg/kg BW of plant extract, there was no toxicity recorded. Based on the toxicity results, 100 and 200 mg/kg BW were given to diabetic rodents for 21 days. *In vivo* evaluation of the extract revealed a decrease in glucose levels with significant improvements in blood glucose levels, serum marker chemicals like SGPT, SGOT, and ALP, at the end of the first, second, and third weeks after hydroalcoholic *Leucomeris spectabilis* extract treatment. According to the results, the hydroalcoholic leaf extract had the greatest impact.[67]

Neolamarckia cadamba
Neolamarckia cadamba belongs to the *Rubiaceae* family. The antidiabetic activity was investigated using a methanol extract from the plant's aerial parts. The experimental rats received a solitary intraperitoneal infusion of 120 mg/kg BW of alloxan monohydrate. For 14 days, methanol extract was administered orally in portions of 250 and 500 mg/kg BW of plant extract. Also, metformin was administered orally at 850 mg/kg BW. The pharmacological mechanism underlying α-amylase inhibition and delayed glucose absorption from the digestive system was discovered. The most noticeable changes were a significant drop in blood glucose levels and an increase in body weight.[68]

Pistachia Khinjuk
Pistachia khinjuk belongs to the Anacardiaceae family. To test the antidiabetic activity, an aqueous methanol fruit extract from the plant was used. Experimental rats were intraperitoneally infused with alloxan at a dose of 150 mg/kg BW. There was no toxicity observed after the oral administration of a dose of 5mg/kg BW of Glibenclamide following alloxan monohydrate and plant extract doses of 2450 and 4243 mg/kg BW. Based on the toxicity results, 500 and 250 mg/kg BW doses of *Pistachia khinjuk* were administered. *Pistachia khinjuk* aqueous methanol extract lowers blood glucose levels. Because of the presence of phenolic constituents, the methanolic extract is an excellent anti-diabetic medication.[69]

Sarcostemma brevistigma
Sarcostemma brevistigma belongs to the family of Asclepiadaceae. Extracts from the young stems (twigs) and leaves were employed to assess the antidiabetic activity of the plant. Malic acid, alpha and beta amyrins, and beta-sitosterol are all found in the plant. Alloxan monohydrate was administered at 150 mg/kg BW as a standard portion through a single intraperitoneal infusion. At a dose of 2000 mg/kg BW of plant extract, there was no toxicity. Based on the toxicity results, oral administration of 250 mg/kg BW once daily was recommended. Insulin levels were significantly increased. *Sarcostemma brevistigma* methanol concentrate can both reduce hyperglycemia and control other blood serum biological parameters.[70]

Sidda cordifolia
Sidda cordifolia belongs to the Malvaceae family. Ethanolic and aqueous extracts from the entire plant were employed to evaluate the antidiabetic action. An intraperitoneal infusion of alloxan (120 mg/kg BW) was given to the experimental rats. At a dose of 2000 mg/kg BW of plant extracts, there was no observable toxicity. Based on the toxicity results, 5, 50, and 300 BW of the plant extracts were administered for 14 days. A 1 mg dose of Glibenclamide was also taken orally. The extracts controlled the blood glucose level, bodyweight reduction, and adjustment of various lipid metabolic enzymes. *Sidda cordifolia* extract has a significant reduction in sugar levels.[71]

Sigesbeckia orientalis
S*igesbeckia orientalis* belongs to the family of Asteraceae. An aqueous extract of the entire *Sigesbeckia orientalis* plant contains bioactive compounds such as flavonoids, phenols, tannins, sesquiterpene lactone, orientin, di-terpenes, and 3,7-dimethyl quercetin. Intraperitoneal infusion of alloxan dosage at 150 mg/kg BW and plant extract at a dose of 2000 mg/kg BW was not associated with

any toxicity. Based on the toxicity results, 250, 500 mg/kg BW, and Glibenclamide at 10 mg/kg were administered. Plant extract treatment groups had significantly lower levels of glucose and lipids, total cholesterol, fatty substances, and low-density lipoprotein. Serum alpha-amylase, high-density lipoproteins, and total body weight were all increased significantly in diabetic rats treated with the plant extract.[72]

Salacial lehmbachii

Salacial lehmbachii belongs to the family of Celastraceae. In evaluating the antidiabetic action, the ethanol stem bark of the plant was used. Alloxan dose at 120 mg/kg BW was administered intraperitoneally. At a dose of 5000 mg/kg BW of plant extract, there was no toxicity. Based on the toxicity results, 100, 200, and 400 mg/kg were administered orally. *Salacial lehmbachii* extract exhibited a significant decrease in blood glucose levels. In the stem bark extract, these parameters were significantly reduced, while high-density lipoproteins were significantly increased.[73]

Uvaria chamaethe

Uvaria chamaethe belongs to the family of Annonaceae. The root ethanol extract of *Uvaria chamaethe* was used to prove its antidiabetic effect. Alloxan was administered intraperitoneally at a dose of 150 mg/kg. The diabetic rodents in each group were given 100, 250, and 400 mg/kg of the concentrate orally every day for 14 days. The dosage of Glibenclamide was 71 µg/kg, in addition to pioglitazone (429 µg/kg). The inhibition of α-amylase and α-glucosidase activities was caused by the plant extract. *Uvaria chamaethe* has an antidiabetic action that may be due to inhibition of α-amylase and α-glucosidase and recovery of pancreatic beta prison cells. Similarly, increasing high-density lipoprotein (HDL) saturated fat levels may reduce the risk of cardiac infection.[74]

Zanthoxylum ovalifolium

Zanthoxylum ovalifolium belongs to the family of Rutaceae. Aqueous ethanolic leaf extract was employed in testing its antidiabetic effect. At a solitary intraperitoneal infusion of alloxan 100 mg/kg BW and plant extract at a dose of 2000 mg/kg BW, there was no toxicity observed. Based on the toxicity results, 200 and 400 mg/kg BW, as well as the standard Glibenclamide portion of 5 and 400 mg/kg BW, were administered for 21 days. The ethanol and aqueous extracts at a high dose of 400 mg/kg BW were more effective at reducing blood glucose levels than at a low dose of 200 mg/kg.[75]

Plants produce the most important metabolites for diabetes management, making herbal medicines safe.[97,98] The World Health Organization has recommended that traditional plant actions for diabetes be evaluated because they are active, non-toxic, and have a low number of side effects.[98,100] The current review demonstrated medicinal plants' influenced antidiabetic properties in streptozotocin and alloxan-induced models. Many studies to date have not been able to explain in detail the area of the plant, the presence of active ingredients, dose, and mode of action of the plants, and the active constituents responsible for the antidiabetic result. Plant products are high in phenols, flavonoids, terpenoids, alkaloids, and other elements that help lower blood sugar levels.[101,102] According to the current review, most plants documented in Nigeria include *Anthocleista djalonensis, Loranthus micranthus, Rothmannia hispida, Axonopus compressus, Uvaria chamaethe, Moringa oleifera, Ocimum gratissimum, Vernonia amygdalina, Melanthera scandens, Afzelia Africana, Heinsiacrinata, Senna alata, Gongronema latifolium, Basella rubra, Sterculia tragacantha, Trigonella foenum graecum, Fadogia agrestis, Caralluma europaea, Aloe megalacantha,* and *Aloe pulcherrima.* The ones reported in Tamilnadu include *Sarcostemma brevistigma, Sidda cordifolia, Borreria hispida, Portulaca grandiflora, Embelia ribes, Gymnema sylvestre, Acorus calamus, Alangium lamarckii, Caesalpinia digyna, Ficus amplissima, Merremia emarginata,* and *Merremia tridentate.* In Pakistan, the medicinal plants with an antidiabetic activity that have been documented include *Cassia sophera, Coccnia grandis, Galium tricornutum, Pistachia khinjuk, Sigesbeckia orientalis, Salacial lehmbachii,* and *Elaeagnus umbellate.* Antidiabetic properties have been reported in China for *Acanthopanax Senticosus, Chaenomeles sinensis, Entada phaseoloides, Morus alba, Ophiopogonis japanicus,* and *Opuntia dilleniid).* Most of the plants that belong to the Rubiaceae family have been reported to have antidiabetic activity (12 species). As shown in Figure 3, about 40% of the leaves of medicinal plants are used in the treatment of diabetes. Further investigations can be focused on the isolation of phytocompounds, which can lead to the discovery of newer antidiabetic agents.

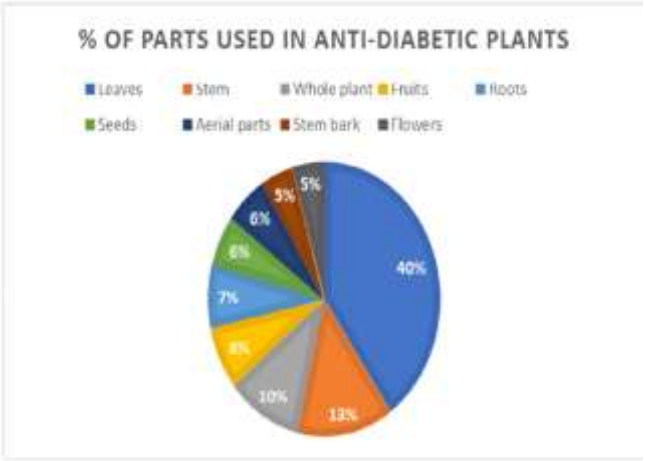

Figure 3: Percentages of the parts of medicinal plants used for antidiabetic agents.

Conclusion

The use of herbal plants for the treatment of diabetes has been addressed in the current review. The majority of the plants are found in Nigeria, Tamilnadu, Pakistan, and China, and seventy herbs have been tested for their effectiveness in the treatment of diabetes.

Herbs, according to the studies, can be used as safer adjuvant medicines in diabetes management and treatment. The majority of plants in the Rubiaceae family have been shown to have antidiabetic properties (12 species). The leaves of medicinal plants are utilized in the treatment of diabetes in about 40% of cases.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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