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REVIEW ON HYPOGLYCEMIC PROPERTIES OF MEDICINAL PLANTS FOR TREATMENT OF DIABETES

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Abstract*:* Diabetes is a significant metabolic illness that is treated with a variety of medicinal herbs in traditional medicine. Many present treatments are derived from these plants, which have no negative effects. According to the World Health Organization, up to 90% of people in underdeveloped countries use traditional medicine (plants and their products) for primary health care. Approximately 800 plants have been identified to have anti-diabetic properties.The goal of this systematic review is to look at diabetes and summaries the many therapies for it, with an emphasis on herbal therapy.

Key words: Diabetes, Herbal treatment, Review, Hypoglycemic properties

Introduction: Diabetes mellitus (DM) is a chronic metabolic disorder, resulting from insulin deficiency, characterized by abnormal increase in the blood sugar level, altered metabolism of carbohydrates, protein and lipids, and an increased risk of vascular complications. Uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis leads to hyperglycemia. Long term damage and failure of different organs were found along with chronic hyperglycemia [1].

As per World Health Organization, DM is a chronic metabolic disorder characterized by common features of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism. There are numerous pathogenic processes involved in the development of diabetes. This includes autoimmune destruction of the β-cells of the pancreas which leads to consequent insulin deficiency and abnormalities that result in resistance to insulin action. Deficiency of insulin on target tissues causes abnormalities in carbohydrate, fat, and proteinmetabolism. It may be due to inadequate insulin secretion and/or diminished tissue responses to insulin. [2] Signs and symptoms of hyperglycemia include polyuria, polydipsia, weight loss, polyphagia, blurred vision, tachycardia, hypotension and wasting. Chronic hyperglycemia may also cause impairment of growth, susceptibility to certain infections. Uncontrolled diabetes causes ketoacidosis of different grades and hyperosmolar (nonketotic hyperglycemic) coma. Its cause is obscure but appears to be precipitated by the same factors as ketoacidosis especially those resulting in dehydration . The development of foot ulcer, renal impairment and retinopathy may be considered as long term complications of long-standing diabetes in a patient[3].

Epidemiology: As of 2010, an estimated 280 million people had diabetes, with type 2 making up about 90% of the cases globally. The incidence of this disease is increasing rapidly and at the end of 2030, the number of cases will be double, as a result of increasing longevity and obesity. Diabetes is more common in developed countries, eventhough there is an increase in the prevalence rate in Asia and Africa. Environmental and genetic factors play an important role in the development of diabetes in varying populations. The incidence of insulin dependent DM ranged from 1.8 to 7.0/100 000 per year in Africa, 0.14 to 10/100 000 per year in Asia, approximately 3.4 to 36/100 000 per year in Europe, 2.61

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to 20.18/100 000 per year in the Middle East and 7.60 to 25.6/100 000 per year in North America and that of non insulin dependent DM ranged from 0.4% to 17.9% in Africa, 1.2% to 14.6% in Asia, 0.7% to 11.6% in Europe, 5.6% to 40% in the Middle East and 7% to 28.2% in North America[4].

Etiologic classification of DM: Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. According to American Diabetes

Pathophysiology of DM: The pathophysiology of diabetes depends on knowledge of the basics of carbohydrate metabolism and insulin action. Carbohydrates from the food are broken down into glucose molecules in the gut and this glucose is absorbed into the bloodstream, elevating the blood glucose levels which results in the secretion of insulin from the pancreatic beta cells. Insulin binding to specific cellular receptors facilitates entry of glucose into the cell. The cell uses glucose for energy production.

The increased insulin secretion from the pancreas and the subsequent cellular utilization of glucose results in lowered of blood glucose levels. Lower glucose levels in turn results in decreased insulin secretion. If insulin production and secretion are altered by diseases, blood glucose dynamics will also change. The decrease in insulin production may inhibit glucose entry into the cells resulting in hyperglycemia. Inadequate utilization of pancreatic insulin by the cells also leads to abnormal increase in the blood sugar level. When there is an elevation in the insulin secretion, blood glucose level becomes low (hypoglycemia) as large amounts of glucose enters the cells and little remains in the bloodstream[5].

Excess glucose is stored in the liver and muscles as glycogen. Later, when energy is needed, glycogenolysis converts stored glycogen back to glucose. Triglycerides also formed from excess glucose and stored in adipose tissue which may subsequently undergo lipolysis, yielding glycerol and free fatty acids. The liver also produces glucose from proteins and fat through a process called gluconeogenesis. Normal homeostasis is achieved through a balance of the metabolism of glucose, free fatty acids and amino acids, which maintains a blood glucose level, sufficient to provide an uninterrupted supply of glucose to the brain. The counter-regulatory hormones such as glucagon, catecholamines, growth hormones, thyroid hormones and glucocorticoids also affect the normal blood glucose level [6].

Type 1 DM : Type 1 diabetes most commonly develop in childhood and progresses with age. It is called as insulin dependent DM. The basic phenomena in the type 1 diabetes is cell-mediated autoimmune destruction of pancreatic beta islet cells. This leads to absolute insulin deficiency and predisposes the individuals to diabetic ketoacidosis (DKA) [7].

Destruction of beta cells and insulin deficiency in a genetically predisposed individual arise from the environmental factors which triggers an autoimmune process is a main feature of type 1 diabetic patients. Several mechanisms contribute to beta cell destruction. T lymphocytes react against beta cell antigens and cause cell damage. The islets show cellular necrosis and lymphocytic infiltration. The lesion is called as insulitis and locally produced cytokines can damage beta cells[8].

Genetic and environmental modifiers causes dysregulation of the immune system and this will lead to the formation of auto antibodies. These antibodies may involve in causing the disease or it may be a result of T-cell mediated cell injury and release of normally sequestered antigens. Autoimmune disorders found with type 1 DM are Graves' disease, pernicious anaemia etc. in about 10%-20% cases[9].

The presence of genetic component in type 1 diabetes involves the inheritance of multiple genes to confer susceptibility to the disorder. Diabetes has a complex pattern of genetic associations, and the susceptibility genes have been mapped to at least 20 loci. In a human leukocyte antigen-associate susceptible individual, beta cells act as autoantigens and activate CD4+ T lymphocytes, bringing about immune destruction of pancreatic beta cells. The environmental factors play an important role in the pathogenesis of type 1 DM. There is an existence of the environmental modifiers of the disease.

Type 2 DM: Type 2 DM previously called non insulin dependent DM or maturity-onset diabetes. It has a late onset and this type comprises about 90% of all cases of diabetes. The two metabolic defects that characterize type 2 diabetes are insulin resistance and inadequate insulin secretion. Type 2 DM is a heterogenous disorder with more complex etiology and is far more common than type 1, but less much known about its pathogenesis[10].

1. Genetics: Multifactorial inheritance is the most important factor in the development of type 2 DM.

Genetic defects of insulin signaling pathway and insulin receptor mediates insulin resistance. Children of type 2 patients show the signs of insulin resistance at an early age. Specific point mutation accounts only for a minority (less than 5%) of patients with the insulin resistance. Analysis of candidate genes have yielded many polymorphisms that associate with type 2 diabetic phenotype, but in most cases the associations have been weak, or the studies were not reproducible[11].

2. Environment: Environmental factors which specifically targets beta cell, triggers the autoimmune process.

3. Beta cell dysfunction : Failures of beta cell function leads to inadequate secretion of insulin, the exact genetic mechanism behind the fall in secretion in these cases are unclear. The possibilities involves amylin which forms fibrillar protein deposits in pancreatic islets, glucose toxicity and lipotoxicity in these cases may worsen the islet cell function[12].

4. Insulin resistance: Insulin resistance is defined as resistance to the effects of insulin on glucose uptake, metabolism or storage. Genetic defects in insulin signaling pathway are not common and if present, are more likely polymorphisms with subtle effects rather than inactivating mutations. The acquired causes of insulin resistance involves nutrition, physical activity and obesity and these are closely associated with each other.

5. Obesity: The link between obesity and diabetes is mediated via effects on insulin resistance[13].

6. Role of free fatty acids: Excess circulating free fatty acids are deposited in the muscle and liver tissues of obese individuals leading to an increase in the level of intracellular triglycerides. These triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state. A decrease in activity of key insulin-signaling proteins mediates the lipotoxic effects of free fatty acids[14].

7. Role of adipokines: A variety of proteins released into the systemic circulation by adipose tissue have been identified. Dysregulation of adipokine secretion may be one of the mechanisms by which insulin resistance is tied to obesity[15].

8. Nutrition: Nutrition plays an important role in the development of obesity, insulin resistance and type 2 diabetes. Increase in the total caloric intake leads to obesity[16].

9. Physical activity: Physical activity is one of the principal therapies to acutely lower blood glucose in type 2 diabetes due to its synergistic action with insulin in insulin-sensitive tissues. Essential hypertension is a common risk factor in patient with type 2 DM. Some studies shows tht regular physical activity lower blood pressure in person with type 2 DM. Weight loss leads to decrease in insulin resistance which may be most beneficial early in progression of the disease[17].

Diagnosis of diabetes and prediabetes

Blood tests are used in the diagnosis of diabetes and prediabetes. Type 2 diabetes may have no symptoms. Currently, the American Diabetes Association recommends routine screening for type 2 DM every 3 years in all adults starting at 45 years of age. Lab analysis of blood is needed to ensure that the test results are accurate. Glucose measuring devices used are not accurate enough for diagnosis but may be used as a quick indicator of high blood glucose. Testing enables to find and treat diabetes before complications occur and to find and treat prediabetes. This can delay or prevent type 2 diabetes from developing. Mass screening programmes have used glucose measurements of fasting, post prandial or random blood sample[18].

- An A1c test, also called the hemoglobin A1c/HbA1c/ glycohemoglobin test;
- A fasting plasma glucose test;
- An oral glucose tolerance test[19].

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause. Not all tests are recommended for diagnosing all types of diabetes. The random plasma glucose test is sometimes used to diagnose diabetes during a regular health checkup and if it measures above 200 µg per deciliter then the individual also shows the symptoms of DM. Main symptoms of diabetes include increased urination, increased thirst, fatigue, weight loss, blurred vision, increased hunger, and diabetic dermadromes. Any test used to diagnose diabetes requires confirmation with a second measurement unless clear symptoms of diabetes exist[20].

1. Urine testing: Urine tests are cheap and convenient, but the diagnosis of urine testing cannot be based on urine testing alone since there may be false positives and false negatives. They can be used in population screening surveys. Urine is tested for the presence of glucose and ketones.

a. Glucosuria

Benedicts qualitative test detects any reducing substance in urine and dipstick method which is more specific and sensitive method.

b. Ketonuria

Rothera's test and Strip test are performed for the detection of ketone bodies[21].

Metabolic complications like ketoacidosis are infrequent.

Complications of DM

1. Acute metabolic complications

a. DKA It is one of the acute metabolic complication of diabetes. DKA is characterized by uncontrolled hyperglycemia, acidosis and increased level of ketone bodies. Decreased effective insulin concentration and increased concentration of counter regulatory hormone lead to ketosis. Patients with ketosis have autoimmune type 1 diabetes. Infection is the most common precipitating factor in the development of DKA[22].

b. Hyperglycemia hyperosmolar state (HHS)

Differences in insulin availability and dehydration due to diuresis distinguishes HHS from ketoacidosis. Sustained hyperglycemic diuresis results in severe dehydration. The patient is unable to drink sufficient water to maintain urinary fluid loss. Plasma osmolality and blood sugar level is very high. HHS is usually seen in patient with type 2 DM. Insulin levels in HHS prevents lipolysis and ketogenesis[23].

c. Hypoglycemia

In those treated for diabetes, a diagnosis of hypoglycemia can be made based on the presence of a low blood sugar alone. The episode may develop in patients with type 1 DM. Alteration of consciousness occurs or even it may lost in extreme cases, leading to permanent brain damage, rebound hyperglycemia and death. The variety of interactions may cause identification difficulty in many instances[24].

d. Respiratory infections

In diabetes patients, alteration in host defence mechanism leads to hyperglycemia, inflammation and increased susceptibility to infections. There is an impairment in the function of respiratory epithelium and ciliary movement[25].

e. Periodontal disease

Diabetes is also associated with gum diseases and may make diabetes more difficult to treat[26].

2. Late systemic complications

a. Atherosclerosis

DM of both type 1 and 2 accelerates the development of atherosclerosis so that consequent lesions appear earlier than in the general population and associated with ulceration, calcification and thrombosis[27].

b. Diabetic microangiopathy

It is characterized by the basement membrane thickening of small blood vessels and capillaries. Thickening is mainly due to the increased glycosylation of haemoglobin and other proteins like collagen and basement membrane material. The pathogenic basis behind microangiopathy is the recurrent hyperglycemia[28].

c. Diabetic nephropathy

Specific renal functional and morphological alterations lead to diabetic nephropathy and are characterized by hyper filtration of glomerulus, albuminuria, renal hypertrophy etc. Initially there is an elevation of renal plasma flow and glomerular filtration rate. Glomerular hypertension and renal insufficiency accelerates kidney failure[29].

d. Diabetic retinopathy

It is a leading cause of blindness. Progression is from mild non proliferative abnormalities to severe proliferative diabetic nephropathy[30].

e. Diabetic neuropathy

It is heterogeneous and may affect all part of the nervous system, but symmetric peripheral neuropathy is most characteristic. It may be local or diffuse[31].

Therapy for DM

Diet therapy is important for the prevention as well as the treatment of all stages of type 2 diabetes. Till it continues to remain high controversial and poorly understood. In majority of the individuals with type 2 DM, if obesity seems along with hyperglycemia, weight reduction is the major goal of dietary therapy. Exercise helps to prevent type 2 DM and control all types of diabetes cases. Muscular sensitivity to insulin can be improved by physical activity. The mechanisms involved are increased blood flow to the tissues and reduced free fatty acid and intra abdominal fat level[32].

Oral hypoglycemic drugs

1. Sulfonylureas and the newer glitinides

Sulfonylureas have been used to treat type 2 diabetes since 1942 and require functional pancreatic beta cells for their hypoglycemic effect. They have an islet beta cytotropic activity. The meglitinides are relatively new class of insulin secretagogues. Both of them act by inducing insulin secretion. The glitinides have a more rapid action of onset and shorter duration of effect than sulfonylureas and are given before a meal to stimulate prandial release of insulin. The average decrease in HgA1c is 1-2 mg/dL. Both these medications can lead to hypoglycemia and weight gain[33].

2. Biguanides-metformin

They stimulate peripheral utilization of glucose, increase the sensitivity of muscle to insulin action and reduce the intestinal absorption of glucose and leads to an average decrease in HgA1c of 1-2 mg/dL by reducing hepatic gluconeogenesis. Patients of renal or hepatic disease, hypoxic pulmonary disease or heart failure are predisposed to lactic acidosis because of reduced drug elimination or reduced tissue oxygenation. Alcohol ingestion may also precipitate lactic acidosis. Metformin is an insulin sparing agent and does not increase weight or provoke hyperglycemia. It should be given first line in obese type 2 diabetics[34].

3. α-glucosidase inhibitors (acarbose and miglitol)

α-Glucosidase inhibitors act by inhibiting absorption of carbohydrates. Acarbose also inhibits α-amylase. On average lower HgA1c by 0.5-1.0 mg/dL. Its use is limited by disagreeable gastrointestinal symptoms. These drugs are contraindicated in patients with inflammatory bowel disease and renal impairment. Acarbose should be used with caution in the presence of hepatic diseases.

4. Thiazolidinediones (rosiglitazone and pioglitazone)

Thiazolidinediones appears to act by binding to the peroxisome proliferator activator receptor-gamma. They increase the peripheral sensitivity to insulin, reduce hepatic glucose output, and increase peripheral glucose disposal[68]. The overall effect on HbA1c is a 1% to 1.5% reduction and they increase high density lipoprotein cholesterol by 3-9 mg/ dL. Glitazones are contraindicated in children, lactating mother, in liver and heart failure cases[35].

5. Incretin mimetic (exenatide)

Exenatide is a long acting glucagon-like peptide-1 analogue. It enhances glucose-dependent insulin secretion. Food and Drug Administration approved for use as an adjunct for those failing oral agents. Major adverse effects include nausea, vomiting and hypoglycemia. It has similar efficacy to bedtime insulin (without the weight gain) when added to failing oral regimen, but substantially more expensive.

6. Amylin analogue (pramlintide)

It suppresses postprandial glucagon secretion and slows gastric emptying. The level HgA1c decreased on average 0.1-0.6 mg/dL. Because of the risk of hypoglycemia insulin doses should be decreased by 50% or more[36].

Insulin

Increase in blood glucose level promotes both synthesis and secretion of insulin from beta cells. Insulin has many formulations. Indications for starting insulin include new diagnosis of severe, symptomatic hyperglycemia, co-morbid conditions such as renal or liver disease, congestive heart failure, active infection that may make control difficult with oral medications, pregnancy, diabetic coma, precoma, and intolerance to oral medications. Formulations of insulin varies in their time to peak activity and duration of action. Patient may need only long-acting insulin in the early stages of type 2 DM. As diabetes progresses will likely need meal time and long-acting insulin to adequately control sugars. Typical starting insulin dose is 10-20 units/d. Therapy has to be individualized and no fixed schedule is possible. Insulin use results in weight gain, allergy, resistance and can lead to hypoglycemia[37].

Plant remedies in the management of DM

1. Acacia arabica

In a study that was done to evaluate the anti-diabetic activity of the acacia plant, oral administration of 200 mg/kg and 100 mg/kg of Acacia arabica bark extract to streptozotocin (STZ)-induced diabetic rats over a 21 days period increased serum insulin. In addition, high serum glucose and insulin resistance decreased, and the lipid profile improved. This plant contains polyphenols, tannins, and flavonoids (for example, quercetin). The presence of these substances with antioxidant properties is an explanation for anti-diabetic effects of this plant. The Acacia arabica extract improves plasma glucose levels, metabolic disorders in lipid metabolism, and oxidative stress in STZinduced diabetic rats . Also, the chloroform extract of Acacia arabica bark was used for 2 weeks in diabetic rats, significantly reduced the blood glucose level and improved the cholesterol, triglyceride, HDL, and LDL levels [38].

2. Achyranthes aspera

The ethanolic extract of Achyranthes aspera leaves (1000 mg/kg) used in STZ-induced diabetic rats significantly reduced their blood glucose level. This is probably due to the inhibition of glucose absorption from the intestine or because of an increase in glucose transport from the blood [39].

3. Acosmium panamense

Oral administration of doses of 200 and 20 mg/kg of aqueous Acosmium panamense extract and 100 and 20 mg/kg doses of butanolic extract of the mentioned herb reduced the plasmas glucose level in STZ-induced diabetic rats within 3 hours. The effects on hypoglycemic for the extract of this plant and glibenclamide (the main drug used to treat diabetes) are similar [40].

4. Aegle marmelose

Oral administration of the aqueous extract dervied from Aegle marmelose fruit (125 and 250 mg/kg) in streptozotocin diabetic Wistar rats twice daily for approximately 4 weeks caused a significant decrease in blood glucose, plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin, alpha-tocopherol, and a considerable increase in plasma reduced glutathione, and vitamin C. The use of a 250 mg/kg dose of the extract was more effective than glibenclamide in the improvement of these parameters. In this research, results clearly show the hypoglycecmic activities of Aegle marmeloseextract [41].

5. Allium sativum (garlic)

Anti-diabetic effects of ethanolic extracts derived from Allium sativum were measured in normal and streptozotocin induced diabetic rats. Oral administration of the ethanolic extract of this plant for 14 days showed a reduction in the level of serum glucose, total cholesterol triglycerides, urea, uric acid, creatinine, AST (aspirate aminotransferase), and ALT (aspirate aminotransferase). However, this extract increased the serum insulin in diabetic rats, but not in normal ones. Comparing the performance of the garlic extract and 600 mg/kg of glibenclamide demonstrated that the anti-diabetic activity of the extract is more effective than glibenclamide [42].

6. Aloe barbadensisMiller

The Aloe barbadensis Miller plant, which is also known as Aloe vera, is used in traditional medicine by many people. Treatment with the ethanolic extract of the fresh leaf gel from this plant (300 and 500 mg/kg) in STZinduced diabetic rats for 42 days resulted in a significant decrease in the fast blood glucose levels. The hypoglycemic effect of this extract can be compared to standard anti-diabetic drugs (glibenclamide and metformin) [43].

7. Andrographis paniculata

Oral administration of ethanolic extract derived from the aerial parts of Andrographis paniculata (different doses of 0.1, 0.2 and 0.4 g/BW) caused a significant reduction in levels of the serum glucose in STZ diabetic rats. However, the effect was not seen in normal rats. This extract and anti-diabetic drugs dramatically reduced the activity of liver glucose-6-phosphatase. Further research has shown that the extract reduces the level of fasting serum triglyceride by 49.8%, while metformin drugs reduces levels by 27.7%, but neither the extract or metformin affect cholesterol levels. In addition, further studies concluded that the ethanolic extract of this plant has anti-diabetic activity that is involved in the increase of glucose metabolism [44].

8. Annona squamosa

The aqueous extract of this plant leaf have many antioxidant effects. The blood glucose, haemoglobin, glycosylated haemoglobin, plasma insulin, antioxidant enzymes, lipid peroxidation in liver and kidneys were examined in STZinduced diabetic rats. Oral administration of Annona squamosa aqueous extract for 30 days caused a significant reduction in the blood glucose, lipids, and lipid peroxidation, but the activity of the plasma insulin and antioxidant enzymes, like catalase and superoxide dismutase, increased. On the other hand, the activity of glutathione and glutathione peroxidase decreased.Generally, the aqueous extract of this plant is useful for controlling blood glucose levels and improving plasma insulin and lipid metabolism. In addition, this extract is effective in preventing diabetic complications caused by lipid peroxidation and antioxidant systems in experimental diabetic rats [45].

9. Argyreia nervosa

Oral administration of ethanolic extract of Argyreia nervosa root (500 mg/kg/BW) decreased blood glucose levels in normoglycaemic rats. While loading rats with oral glucose for 2 hours, the glucose levels decreased from 118.45.4 to 96.44.2 mg/dl. After the consumption of the extract for 7 days in STZ diabetic rats, a significant antihyperglycemic effect occurred [46].

10. Artemisia herba

Oral administration of aqueous extract derived from the aerial parts of this plant (0.39 g/kg/BW) for 2-4 weeks in diabetic rats and rabbits caused a significant reduction in glucose levels and prevented an increase in the levels of glycosylated haemoglobin. Furthermore, this plant has hypoliposis effects and can prevent weight loss in diabetic animals [47].

11. Averrhova bilimbi

The hypolipidemic and hypoglycemic activity of ethanolic extract of Averrhova bilimbi leaves (ABE) was investigated using STZ-induced diabetic rats. Diabetic rats were treated with distilled water, ABE (125mg/kg), or metformin (500mg/kg) twice a day for two weeks. Like metformin, ABE, in comparison with distilled water, significantly reduced the blood glucose level by 50% and the triglyceride level by 130%. In addition, ABE, in comparison with distilled water, increased the concentration of HDL-cholesterol by 60%. It is important to note that the extracts, like metformin, had no effects on the concentration of cholesterol and LDL-cholesterol,

but significantly decreased levels of lipid peroxidation. Research has revealed that ABE has hypoglycemic, hypotriglyceridemic, anti-lipid per oxidative, and anti-atherogenic activities in STZ-induced diabetic rats

12. Azadirachta indica

Administration of the leaf extract and seed oil for 4 weeks reduced the blood glucose levels in alloxan diabetic rabbits. This extract had similar effects as the anti-diabetic drug glibenclamide. The neem extract can control blood glucose and appears to be helpful in preventing or delaying the onset of diabetes . In another study, the antidiabetic effects of the neem was evaluated and it was found that the administration of a single dose of aqueous extract of the bark and root (250 mg/kg) can decrease urea (13%), triglycerides (32%), cholesterol (15%), glucose (18%), lipids (15%), and creatinine (23%) in diabetic rats (24) for 24 hours after treatment.

13. Barleria prionitis

Anti-diabetic activities of Barleria prionitis were studied in normal and alloxan induced diabetic rats. The use of the alcoholic extract of this leaf (200 mg/kg) for 14 days created a significant reduction in blood glucose and glycosylated hemoglobin levels, while a substainal increase occurred in the levels of insulin and liver glycogen. This extract prevented weight loss in the experimental subjects. In another study, the extract of the plant leaves and roots lead to a significant decrease in blood glucose level in diabetic rats [48].

14. Biophytum sensitivum

The Biophytum genus from the Oxalidaceae family is also known as a life plant. The extract of this plant has amino acids, steroids, terpenes, tannins, saponins, flavonoids, polysaccharides, oil essential, and pectin. Studies assessing the hypoglycemic activity of Biophytum sensitivum showed that oral administration of this plant (200 mg/kg) for approximatly 28 days can lead to a significant decrease in blood glucose and glycosylated haemoglobin levels in normal and steptozotonic-nicotinamide-induced diabetic rats. Also, it can cause a significant increase in the total hemoglobin, plasma insulin, and liver glycogen in diabetic rats. Due to the extract effects, the activity of glucose 6phosphatase increased, and fructose- 1-6 bisphosphatase activity was reduced in diabetic rats [49].

15. Brassica nigra

In a recent study, the anti-diabetic activity of this plant was obvious. Treatment of STZ-induced diabetic rats with aqueous extract of the seed (200mg/kg/BW) once a day for 30 days decreased the fasting blood glucose level. In addition, there was a poor increase in the glycosylated hemoglobin and serum lipids levels for the treated group [50].

16. Bryonia alba

Laboratory studies state that oral administration of ethanolic extract of Bryonia alba root (200mg/kg) for 7 days causes a significant decrease in glucose level in alloxan-induced diabetic rats. Also, these studies confirmed the historic claims about the anti-diabetic activity of the plant [51].

17. Caesalpinia bonducella

This plant has anti-nociceptive, anxiolytic, anti-filarial, and anti-diarrhoeal activities. Phytochemical analysis determined the presence of alkaloids, flavonoids, glycosides, saponins, tannins, and triterpenoids in this plant . Oral administration of the plant seed extract (300mg/kg) caused a tangible anti-hyperglycemic effect in alloxaninduced hyperlipidemia and decreased the BUN level. This extract caused a significant reduction in cholesterol levels and increased LDL levels in diabetes induced hyperlipidemia. The anti-diabetic actions of the extract is thought to be due to glucose absorption blockage [52].

18. Cajanus cajan

This plant is used in Panamanian culture as a medicinal plant for treating diabetes. Different parts of the plants are used in Africa, Asia, and South America to control disorders, including ulcer, diarrhea, pain, diabetes, cough, and sores. Among the four tested extracts of this plant, viz petroleum ether, choloroform, ethyl aceate, and methanol extract, only ethyl acetate and methanolic extracts decreased glucose levels, and reached 27.09% and 37.68% by oral administration of 250mg/kg for 10 days in diabetic mice. Also, insulin decreased blood glucose levels by 32.66%. These two extracts increased insulin activity and the simultaneous use of ethyl acetate and methanolic extracts caused a reduction in blood glucose levels, by 43.07% and 48.14%, respectively. It was concluded that these two extracts of the Cajanus cajan plant are more likely to have anti-diabetic bioactive components [53]

Conclusion: In conclusion, this research provided a list of anti-diabetic plants that can be utilised to treat diabetes mellitus. It was discovered that these plants have hypoglycaemic properties and can be utilised to treat a variety of diabetes-related issues. Plants have long been a valuable source of medicine for the treatment of a variety of diseases, but many plants and active chemicals derived from them are still poorly understood. This study

concluded with a list of anti-diabetic plants that can be used to treat diabetes mellitus. These plants have been revealed to have hypoglycaemic characteristics and can be used to treat a number of diabetes-related problems. Plants have long been a vital source of medicine for treating a range of ailments, but many of them, as well as the active compounds derived from them, are still poorly understood.

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