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THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF PLANTS WITH ANTIDIABETIC EFFECTS (PART 1)

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ABSTRACT

Previous studies showed that a wide range of medicinal plants exerted antidiabetic effects. These plants included: *Achillea santolina*, *Adiantum capillus-veneris*, *Agrimony eupatoria*, *Agropyron repens*, *Allium cepa*, *Allium sativum*, *Aloe vera*, *Alpinia galangal*, *Althaea officinalis*, *Anchusa strigosa*, *Anthemis nobelis*, *Arctium lappa*, *Artemisia campestris*, *Asparagus officinalis*, *Avena sativa*, *Ballota nigra*, *Benincasa hispida*, *Brassica nigra*, *Brassica rapa*, *Bryophyllum calycinum*, *Caesalpinia crista*,*Calotropis procera*, *Canna indica*, *Capparis spinosa*, *Capsicum annuum*, *Capsicum frutescens*, *Carum carvi*, *Carthamus tinctorius*, *Cassia occidentalis* and *Casuarina equisetifolia*. This review was designed to highlight the antidiabetic effects of these medicinal plants.

Keywords: Medicinal plants, Antidiabetic, Pharmacognosy, Pharmacology.

INTRODUCTION

Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Chemical analysis showed that Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [1-45]. Recent pharmacological studied revealed that plant constituents act as antidiabetic. This paper was designed to highlight the antidiabetic effects of the medicinal plants.

Achillea santolina

An acute administration of the aqueous extract of *Achillea santolina* (in a dose of 150 and 250 mg/kg body weight orally) resulted in significant reductions of serum glucose level in streptozotocin -induced diabetic rats. Chronic administration of the aqueous extract of *Achillea santolina* in a dose of 250 mg /kg orally for 28 days also showed marked hypoglycemic effects in streptozotocin -induced diabetic rats in comparison with diabetic control group [46].

Adiantum capillus-veneris

When the total extract of the plant prepared by boiling the dried material with water was given to mice (25 mg/kg) orally, it reduced glucose-induced hyperglycemia. However, the extract of the plant prepared by maceration with 80% ethanol, showed no hypoglycemic activity when given to mice in a dose of (25 mg/kg) orally [47]. The alcoholic extract of *Adiantum capillus-veneris* showed significant hypoglycaemic effect in rabbit model, started after 30 min of administration of the extract and continued for 4 hours [48]. El-Tantawy *et al*., recorded the antidiabetic and diuretic effects of the alcohol and aqueous extracts of *Adiantum capillus-veneris* as well as its isolated mucilage [49].

Agrimony eupatoria

The effects of dietary administration of *Agrimony eupatoria* on streptozotocin (STZ)-diabetic mice and on *in vitro* glucose uptake, glucose metabolism and on insulin secretion by BRIN-BD11 cells were investigated. Agrimony incorporated into the diet (62.5 g/kg) and drinking water (2.5 g/l) countered the weight loss, polydipsia, hyperphagia and hyperglycaemia of STZ-diabetic mice. Aqueous extract of agrimony (1 mg/ml) stimulated 2-deoxy-glucose transport (1.4-fold), glucose oxidation (1.4-fold) and incorporation of glucose

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into glycogen (2.0-fold) in mouse abdominal muscle comparable with 0.1 microM-insulin. In acute 20 min tests, 0.25-1 mg/ml aqueous extract of agrimony evoked a stepwise 1.9-3.8-fold stimulation of insulin secretion from the BRIN-BD11 pancreatic B-cell line. This effect was abolished by 0.5 mM-diazoxide and previous exposure to extract did not adversely affect subsequent stimulation of insulin secretion by 10 mM-L-alanine, thereby indicating that there was no detrimental effect of the extract on cell viability. The effect of extract was glucose-independent and was not evident in BRIN-BD11 cells exposed to a depolarizing concentration of KCl. The ability of agrimony extract to enhance insulin secretion was dependent on use of heat during extract preparation. These results indicate the presence of antihyperglycaemic, insulin-releasing and insulin-like activity in *Agrimony eupatoria* [50].

Agropyron repens

The hypoglycaemic effect of an aqueous extract of *Agropyron repens* (*Triticum repens*) rhizomes was investigated in normal and streptozotocin (STZ) diabetic rats. After a single oral administration of the aqueous extract (20mg/kg) a significant decrease on blood glucose levels in STZ diabetic rats ($p<0.001$) was observed; the blood glucose levels were normalized after 2 weeks of daily oral administration of aqueous extract (20mg/kg) ($p<0.001$). Significant reduction on blood glucose levels were noticed in normal rats after both acute ($p<0.001$) and chronic treatment ($p<0.001$). In addition, no changes were observed in basal plasma insulin concentrations after treatment in either normal or STZ diabetic rats indicating that the underlying mechanism of this pharmacological activity seems to be independent of insulin secretion [51].

Allium cepa

The ethanol, chloroform and petroleum ether extracts of *Allium cepa* exerted hypoglycemic effects in alloxan, glucose and epinephrine induced diabetes in experimental animals [52-59]. The aqueous extract of onion , as well as its hypoglycemic effects, it improved the reduction in the antioxidant parameters (superoxide dismutase, catalase, glutathion peroxidase, and reduced glutathione) in alloxan induced diabetic rabbits [60]. In assessment of hypoglycemic activity of *Allium cepa* in type 1 and type 2 diabetic patients, ingestion of crude *Allium cepa* (100 g) caused a considerable reduction in fasting blood glucose levels by about 89 mg/dl in relation to insulin (145 mg/dl) in type 1 diabetic patients and it reduced fasting blood glucose levels by 40 mg/dl, compared to glibenclamide (81 mg/dl) in type 2 diabetic patients, 4 hours later. The same dose of crude *Allium cepa* produced a significant reduction in the induced hyperglycemia (GTT) by about 120 mg/dl compared to water (77 mg/dl) and insulin (153 mg/dl) in type 1 diabetic patients and considerably reduced GTT by 159 mg/dl in relation to water (55 mg/dl) and glibenclamide (114 mg/dl) in type 2 diabetic patients, after 4 hours [61]. The mechanisms that mediate the hypoglycemic effects of *Allium cepa* were included: Alyl propyl disulfide compounds competed with insulin for metabolism resulting in an increase of free insulin. *Allium cepa* also facilitated glycogen storage and increased glutathione peroxidase . Sulfur containing compounds such as dialkyl disulfides and their oxidized thiols can trap electrons from other systems and act as antiuoxidants. In addition , phenolic acids such as caffeic, chlorogenic ,ferulic, sinapic, p-coumaric, vanillic, syringic and p-hydroxy produced antioxidant activity [60-61].

Allium sativum

Garlic has been found to be effective in lowering serum glucose levels in streptozotocin and alloxan-induced diabetes in rabbits, rats and mice [62-64]. S-allyl cysteine sulphoxide, (allicin) in a dose of 200 mg/kg body weight was significant antidiabetic in rats [65, 66]. However**,** both garlic oil and diallyl trisulphide produced hypoglycemic effects and improved glycaemic state in streptozotocin -induced diabetes in rats [67]. Orally administered garlic juice resulted in better utilization of glucose in glucose tolerance tests in rabbits. Allicin produced 60% of the activity of tolbutamide in alloxan-induced diabetic rabbits at a dose of 250 mg/kg [68]. Oral administration of garlic powder (800mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6 % [69]**.**

Aloe vera

Aloe gel decreased blood sugar in diabetic and normal mice. It also decreased insulin resistance in mice [70-73]. In clinical trials, it appeared that orally administered *Aloe gel* (1-2 tablespoons twice daily) enhanced the hypoglycemic effect of glibenclamide [74-75].

Alpinia galanga

The administration of powdered rhizome of *Alpinia galanga* to the normal rabbits produced significant decrease in blood glucose level [76]. However Srividya *et al* found that the ethanolic extract of *Alpinia galanga* exerted antidiabetic effects in rats. The glucose uptake by rat hemi diaphragm was significantly more in all groups tested compared to control. 400 mg/kg b.wt treated group showed marked increase in body weight. Fluid intake (ml/day) was also increased when compared to the diabetic control. Serum glucose level (mg/dl) was found to decrease gradually from the date of administration of the extract to the end of the study when compared to the diabetic control. 400 mg/kg bw in diabetic rats showed potent serum glucose reducing capacity than 200 mg/kg bw. Total protein level was

found to increase in the extract treated group when compared to diabetic control. Serum triglyceride level was found to be decreased when compared with diabetic control as well as diabetes treated with glibenclamide. Total cholesterol was also found to decrease drastically on the administration of the extract when compared with the diabetic control. The ethanolic extract of *Alpinia galanga* was found to be effective in inhibiting the α-Glucosidase when compared to Acarbose [77].

Althaea officinalis

Polysaccharide from the root of *A. officinalis* (Althaea mucilage-O) administered intraperitoneally to nondiabetic mice significantly reduced blood glucose [78]. Scopoletin (7-hydroxy-6-methoxy coumarin) is therapeutically evaluated in rats for hyperglycemia. Scopoletin (1.00 mg/kg, p.o.) administered daily for 7 days decreased the levels of serum thyroid hormones and glucose [79]**.**

Anchusa strigosa

The antidiabetic activity of aqueous extract of flowers of *A. strigosa* was examined in streptozotocin induced diabetic rats. The aqueous extract of *A. strigosa* flowers in a dose of 250 mg/kg and 500 mg/kg administered orally to diabetic rats for 30 days caused a dose-dependent fall in blood glucose and an improvement in serum insulin levels. Cholesterol and triglyceride levels showed significant reduction in comparison with diabetic control group. The extract treatment also showed significant increase in hepatic glycogen levels [80].

Anthemis nobelis

The effect of both a single dose and daily oral administration dose (20mg/kg body weight) for 15 days of the aerial part of *Chamaemelum nobile* aqueous extract on blood glucose concentrations and basal insulin levels in normal and streptozotocin-induced diabetic rats (STZ) were studied. Single oral administration of *C. nobile* aqueous extract reduced blood glucose levels from 6.0 ± 0.3 mmol/l to 4.9 ± 0.09 mmol/l ($P < 0.05$) 6h after administration in normal rats and from 21.1 ± 1.3 mmol/l to 14.5 ± 0.9 mmol/l ($P < 0.001$) in STZ diabetic rats. Furthermore, blood glucose levels were decreased from 6.1 ± 0.06 mmol/l to 4.6 ± 0.17 mmol/l ($P < 0.01$) and from 21.1 ± 1.31 mmol/l to 13.7 ± 0.9 mmol/l ($P < 0.01$) in normal and STZ diabetic rats, respectively, after 15 days of treatment. Basal plasma insulin concentrations remain unchanged after treatment in both normal and STZ diabetic rats , which means that the mechanism of this pharmacological activity seems to be independent of insulin secretion [81]. Flavonoid glucoside chamaemeloside, has been determined to have in vivo hypoglycaemic activity [82].

Arctium lappa

The antidiabetic effect of the ethanolic extract of the root of burdock (*Arctium lappa* L.) was investigated in streptozotocin- induced diabetic rats. Oral administration of the root ethanolic extract was significantly decreased blood glucose and increased insulin level in diabetic rats compared to the control diabetic group. Meanwhile, the levels of serum total cholesterol , triglycerides and low density lipoprotein in the root ethanolic extract treated diabetic rats were lower, and the high density lipoprotein level was higher than those index of the control diabetic rats. Furthermore, oral administration of root ethanolic extract was significantly decreased serum urea and creatinine as well as malondialdehyde levels of liver and kidney tissues, while body weight gain and tissue glycogen content were elevated in diabetic rat, all of which indicate an improvement in diabetic state. In addition, 400 mg/kg body weight of root ethanolic extract had a marked improvement of the glucose tolerance in normoglycemic rats [83]. Silver *et al* investigated the effect of burdock powder on normal and diabetic patients, and found out that burdock root possess hypoglycemic effects. The antidiabetic effects of burdock root was related to polysaccharides, the main component of the root . Root extract maintained the blood glucose level constant, therefore improving the tolerance to high glucose level [84].

Artemisia campestris

The effects of aqueous extracts of *A. campestris* leaf aqueous extract was examined on glycemic state , lipid profile, lipid peroxidation (MDA), protein carbonyl content (PCO), advanced oxidation protein products (AOPP), activities of both non-enzymatic and enzymatic antioxidants in alloxan-induced diabetic rats. The administration of *A. campestris* to diabetic rats at a dose of 200 mg kg^{-1} bw resulted in a significant reduction in glycemia, TC, TG, LDL-c, pancreas LPO, PCO and AOPP levels, CAT and GPx activities associated with an elevation of GSH content and SOD activity in comparison with diabetic group [85].

Asparagus officinalis

Streptozotocin-induced diabetic rats were treated with a methanolic extract of *Asparagus officinalis* seeds (250 and 500 mg/kg per d) or glibenclamide for 28 days. Treatment of the diabetic rats with the *Asparagus officinalis* extract at doses of 250 and 500 mg/kg suppressed the elevated blood glucose in a dose- and time-dependent manner. The 500 mg/kg, but not 250 mg/kg, dose significantly improved serum insulin levels in the diabetic rats. The insulin: glucose ratio was significantly increased at both doses in the *A. officinalis*-treated rats. Both qualitative and quantitative improvements in β-cell function were found in the islets

of the *A. officinalis*-treated rats. The extract showed potent antioxidant activity in an *in vitro* assay and also improved the total antioxidant status *in vivo*. In most cases, the efficacy of *A. officinalis* (500 mg/kg) was very similar to a standard anti-diabetic drug, glibenclamide [86]. The hypoglycaemic effect of the aqueous extract of asparagus by-product (AEA) was evaluated in a streptozotocin (STZ)-induced diabetic rat model. Continuous administration of AEA for 21 days significantly decreased fasting serum glucose and triglyceride levels but markedly increased body weight and hepatic glycogen level in diabetic rats. In an oral glucose tolerance test, both the blood glucose level measured at 30, 60 and 120 min after glucose loading and the area under the glucose curve showed a significant decrease after AEA treatment [87].

Avena sativa

The treatment with *Avena sativa* caused an increase of insulin activity and improving sensitivity for normalizing blood glucose level and reduce glucose production by the liver [88]. The glycaemic and insulinaemic response to oat bread, oat bread with lingonberry fibre, oat-buckwheat bread and buckwheat porridge were tested in a small-scale clinical study (KHSHP E514/09). Nine healthy volunteers consumed test foods after overnight fasting. From samples taken at seven time points during 120 min. The mean glycaemic and C-peptide indexes (C-pepIs) were 32 and 100 for oat bread, 47 and 119 for oat-lingonberry fibre bread, 58 and 105 for oat-buckwheat bread and 71 and 77 for buckwheat porridge [89]. Oat and barley foods have been shown to reduce human glycaemic response, compared to similar wheat foods or a glucose control. Regression analysis on 119 treatments indicated that change in glycaemic response (expressed as incremental area under the post-prandial blood-glucose curve) was greater for intact grains than for processed foods. For processed foods, glycaemic response was more strongly related to the β-glucan dose alone ($r(2)=0.48$, $P<0.0001$) than to the ratio of β-glucan to the available carbohydrate ($r(2)=0.25$, $P<0.0001$). For processed foods containing 4 g of β-glucan, the linear model predicted a decrease in glycaemic response of 27 ± 3 mmol / min/l. Thus, intact grains as well as a variety of processed oat and barley foods containing at least 4 g of β-glucan and 30-80 g available carbohydrate can significantly reduce post-prandial blood glucose [90].

Ballota nigra

The hypoglycemic effect of *Ballota nigra* extract was investigated in Alloxan-induced diabetes mellitus in rats. Administration of aqueous extract of *B. nigra* extract significantly reduced glucose in both healthy and diabetic rats [91].

Benincasa hispida

The stem chloroform extract of *Benincasa hispida* has significant hypoglycemic activity in normal male Wistar rats. The maximum reduction in blood glucose levels with stem extract of *Benincasa hispida* was recorded at a dose of 200 mg/kg bw [92].

Salad was prepared by using 100gm of ash gourd (*Benincasa hispida*) and one gram of curry leaves (10 curry leaves) and five grams of skimmed milk powder (made into curd) and pepper and salt are added for taste. This salad was freshly prepared every day and given to hyperlipidemic diabetic patients in mid morning for a period of three months to find out the therapeutic effect of supplementation of ash gourd and curry leaves. Supplementation of ash gourd and curry leaves had significant hypoglycemic and hypolidemic effect and it reduced the blood glucose level (both fasting and post prandial), within the period of three months [93, 94]. *Benincasa hispida* in a dose of 250 and 500 mg/kg in mice induced dose dependent decrease in glucose, triglyceride and insulin levels in plasma. It was also increased the glucose uptake from hemidiaphragm [95].

Brassica nigra

In streptozotocin induced diabetic rats treated with aqueous, ethanol, acetone and chloroform extracts of the seeds of *Brassica nigra*, the increase in serum glucose value between 0 and 1 hr of glucose tolerance test (GTT) was the least (29 mg/dl) in aqueous extract treated animals, while it was 54, 44 and 44mg/dl with chloroform, acetone and ethanol extracts respectively. In addition the effective dose of aqueous extract was found to be 200 mg/kg body weight in GTT. Administration of 200 mg/kg body weight of aqueous extract to diabetic animals once daily for one month brought down fasting serum glucose (FSG) levels . The glycosylated hemoglobin (HbA1c) and serum lipids in the treated group were much less than untreated diabetic controls [96]. Aqueous extract of *Brassica nigra* (AEBN) has been shown to have good antidiabetic effect along with significant decrease ($p<0.01$) of abnormal serum lipid levels. The mechanism of this effect was studied via investigation the effect of oral administration of AEBN for two months on glycolytic and gluconeogenic enzymes in liver and kidney tissues of rats with streptozotocin (STZ) induced diabetes mellitus. The activities of gluconeogenic enzymes were higher and of glycolytic enzymes were decreased in both the liver and kidney tissues during diabetes. However, in diabetic rats treated with AEBN for two months, decrease of serum glucose, increase of serum insulin and release of insulin from pancreas (shown in vitro from isolated pancreas) along with the restoration of key regulatory enzyme activities of carbohydrate metabolism and glycogen content were observed. The therapeutic role of AEBN in STZ induced diabetes can be attributed to the release of insulin from

pancreas and change of glucose metabolizing enzyme activities to normal levels, thus stabilizing glucose homeostasis in the liver and kidney. The LD50 was found to be more than 15 times the effective dose (ED) implying higher margin of safety for AEBN [97].

Brassica rapa

The antidiabetic efficacy of turnip (*Brassica rapa*) roots ethanol extract (TE) was investigated in type 2 diabetic animals. C57BL/KsJ-db/db (db/db) mice and db/+ mice were used and the db/db mice were divided into control, TE (0.26 g/100g diet) and rosiglitazone (RG, 0.005 g/100g diet) groups. Despite hyperinsulinemia, the glucokinase activity was lower in the liver of the db/db mice than the db/+ mice, while the glucose-6-phosphatase activity was higher. TE and RG improved the glucose and insulin tolerance and lowered the blood glycosylated hemoglobin, plasma insulin, C-peptide and glucagon levels as well as reversed these hepatic glucose regulating enzyme activities in db/db mice. TE also increased the insulin/glucagon ratio and hepatic glycogen content. The plasma free fatty acid and plasma and hepatic cholesterol and triglyceride levels were higher in the db/db mice than db/+ mice. Interestingly, TE and RG lowered these plasma and hepatic lipids, and simultaneously reduced the hepatic phosphatidate phosphohydrolase, HMG-CoA reductase, ACAT, beta-oxidation and carnitine palmitoyl transferase activities. Furthermore, TE lowered the hepatic fatty acid synthase activity, hepatic lipid droplets accumulation, and adipose tissue weight and size [98].

Bryophyllum calycinum

The aqueous extract of *B. pinnatum* caused significant reductions in the blood glucose levels of the fasted normal and fasted streptozotocin –treated diabetic rats [99-101].

Caesalpinia crista

The seed powder, dissolved in water, showed hypoglycaemic activity in alloxanized hyperglycaemic rabbits. The aqueous extract of the seeds produced similar effects in rats [102]. *Caesalpinia crista* seed extract 300mg/kg orally produced significant anti hyperglycemic action , and decreased blood urea nitrogen levels significantly. It also induced hyperlipidemic effects significantly by lowering the elevated cholesterol and LDL level. The anti-hyperglycemic action of the extracts may be due to the blocking of glucose absorption [103]. The seed kernel powder was reported to have hypoglycaemic activity in experimental animals. Four extracts (petroleum ether, ether, ethyl acetate and aqueous) were tested for their hypoglycaemic potentials in normal and alloxan induced diabetic rats. In normal rats, only ethyl acetate and aqueous extracts showed minimum significant hypoglycaemic effect. In diabetic rats, the ether extract showed a marginal antidiabetic activity, while the petroleum ether extract failed to showed significant hypoglycaemic effect [104]. The antidiabetic activity of ethanolic and aqueous seed extracts of *Caesalpinia crista* were evaluated in streptozotocin induced diabetes in 2 days old pup's models. Both ethanolic and aqueous seed extracts of *Caesalpinia crista* showed antidiabetic activity, but the aqueous extract of *Caesalpinia crista* showed more significant effect as compared to the ethanolic extract. Both extracts caused significant decrease in serum glucose, cholesterol and triglyceride when compared with diabetic untreated group after 3 weeks treatment. Treatment with the extracts also affected the physical parameters; they decreased body weight, increase demand of food and water intake when compared with diabetic untreated group [105]. Hypoglycaemic, antihyperglycaemic and hypolipidemic activities of the aqueous and 50% ethanolic extracts of *Caesalpinia crista* seeds were studied in normal and streptozotocin - diabetic rats. In normal rats, both extracts exhibited hypoglycaemic activity as early as 4 h after administration at a lower dose (100 mg/kg). The hypoglycaemia produced by the aqueous extract was of prolonged duration as compared to ethanolic extract. In diabetic rats, both extracts produced significant ($P < 0.01$) antihyperglycaemic effect from day 5 onwards. Aqueous extract also exhibited antihypercholesterolemic and antihypertriglyceridemic effects in streptozotocin-diabetic rats [106]. The hydromethanolic extract was administered orally at a dose of 250 mg/kg of body weight per day to streptozotocin-induced diabetic rats for 21 days. The effects of hydromethanolic extract on the fasting blood glucose (FBG) level, activities of key carbohydrate metabolic enzymes like hexokinase, glucose-6-phosphatase, and glucose-6-phosphate dehydrogenase, and antioxidant enzymes like catalase and superoxide dismutase along with the effect on the lipid peroxidation level in hepatic tissues were studied. Glycogen levels were also assessed in hepatic and skeletal muscles and some toxicity parameters, such as serum glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and alkaline phosphates activities were also measured. Treatment of the hydromethanolic extract of the seeds of *Caesalpinia crista* resulted in a significant ($P < 0.05$) recovery in the activities of carbohydrate metabolic enzymes along with correction in FBG and glycogen levels as compared with the untreated diabetic group. The extract also caused significant ($P < 0.05$) recovery in the activities of toxicity assessment enzyme parameters. The corrective effects produced by the extract were comparable to the standard antidiabetic drug, glibenclamide [107].

Calotropis procera

The root extracts of *Calotropis procera* were investigated for its anti-hyperglycemic effect in Male

Wister Albino rats. Glibenclamide 500 µg/kg, petrolium ether, methanol and aqueous extracts of roots of *C. procera* were administered to streptozotocin induced diabetic rats at a dose of 250 mg/kg bw as a single dose per day for 15 days. It appeared that methanol and aqueous extracts were the most effective hypoglycemic extracts [108]. The protection effects of the dried latex of *Calotropis procera* against alloxan induced changes in rat kidney was evaluated. Daily oral administration of the aqueous suspension (100 and 400 mg/kg) in diabetic rats produced anti-hyperglycemic effect that was comparable to that of glibenclamide (10 mg/kg). Unlike glibenclamide, the aqueous suspension did not increase the serum insulin levels in diabetic rats. However, it produced a marked reduction in the levels of urinary glucose and protein and normalized the renal tissue levels of thiobarbituric acid-reactive substances (TBARS) and glutathione (GSH) in diabetic rats and the effect was comparable to that of glibenclamide. The protection afforded by the aqueous suspension was also evident from the histological analysis of the renal tissue [109]. Chronic administration of root methanol, stem methanol and leaf ethyl-acetate extracts of *Calotropis procera* for 2 weeks at 100 and 250 mg/kg doses were significantly ($p<0.01$) attenuated the diabetes induced mechanical hyperalgesia, thermal hyperalgesia, tactile allodynia and HbA1C% level in streptozotocin diabetic rats as compared to negative control rats. Furthermore, the root methanol extract of *Calotropis procera* in a dose of 100mg/kg enhanced the regeneration capability of β cells in the pancreas with significant ($p<0.01$) improvement in plasma insulin level in streptozotocin diabetic rats compared to untreated control rats [110]. The dry latex was evaluated for its antioxidant and antihyperglycemic effects in rats with alloxan-induced diabetes. Daily oral administration of dry latex at 100 and 400 mg/kg produced a dose-dependent decrease in blood glucose and an increase in hepatic glycogen. It also prevented the body weight loss in diabetic rats and reduced the daily water consumption to values comparable with those of normal rats [111].

Canna indica

The polyphenolic compounds from *Canna indica* L. root increased glucose transport in cultured muscle cells [112].

Capparis spinosa

The antidiabetic hypolipidemic effect of *Capparis spinosa* fruit extract was studied in diabetic rats (200mg/kg and 400mg/kg bw) for 28 days, these doses caused nonsignificantly decreases in the glucose level at 60 and 120 min. However, *Capparis spinosa* extract exerted lipid lowering effects with the same extract [113]. The effects of *Capparis spinosa* fruit on histomorphological changes in pancreas in streptozotocin induced diabetes in male rats were studied . Histological assessments showed a significant increase in the number of β cells, diameter of islets, and amount of insulin in groups treated with hydroalcoholic extract of *Caparis Spinosa* compared to the diabetic control group [114, 115].

Capsicum annuum and ***Capsicum frutescens***

Capsaicin exhibited a hypoglycaemic effect in dogs; insulin release was increased [116].

Carum carvi

The effect of single and repeated oral administration of the aqueous extract of *Carum carvi* fruits at a dose of (20mg/kg) on lipid metabolism was studied in normal and streptozotocin-induced diabetic rats (STZ). After a single oral administration, *Carum carvi* extract produced a significant decrease on triglycerides levels in normal rats ($p<0.05$). In STZ diabetic rats, cholesterol levels were decreased significantly 6h after *Carum carvi* treatment ($p<0.05$). On the other hand, repeated oral administration of *Carum carvi* extract exhibited a significant hypo-triglyceridemic and hypo-cholesterolemic activities in both normal ($p<0.01$) and STZ diabetic rats ($p<0.001$), 15 days after *Carum carvi* treatment [117]. The hypoglycemic effect of caraway ethanolic extract was investigated in normal and streptozotocin-induced diabetic rats. The results showed that the caraway ethanolic extract seeds at doses 0.2, 0.4 and 0.6 g/kg body weight significantly decreased serum glucose in diabetic rats in 3 and 5 h, but not in healthy rats [118]. To evaluate the effect of oral administration of caraway on the blood glucose level and the weight of diabetic rats. Diabetes was induced by intraperitoneal injection of 60 mg/kg body weight streptozotocin. Caraway was given orally at a dose of 1g/kg body weight daily. The results showed that oral administration of caraway caused a significant decrease in blood glucose level ($p=0.001$) and alleviated their body weight loss ($p=0.037$) [119]. The hypoglycaemic effect of aqueous extracts of *Carum carvi* was investigated in normal and streptozotocin (STZ) diabetic rats. Single dose or 14 days oral administration of the aqueous extracts (20 mg/kg) produced significant decrease in blood glucose levels in STZ diabetic rats ($P<0.001$); the blood glucose levels were nearly normalized 2 weeks after daily repeated oral administration of aqueous extracts (20 mg/kg) ($P<0.001$). No highly significant changes on blood glucose levels were noticed in normal rats after both acute and chronic treatments with extract. In addition, no changes were observed in basal plasma insulin concentrations after treatment with aqueous extract in either normal or STZ diabetic rats, which indicate that the underlying mechanism was doesn't depend of insulin secretion [120].

Carthamus tinctorius

The antidiabetic effect of *Carthamus tinctorius* was studied on fasting blood glucose and insulin levels in alloxan induced diabetic rabbits. Diabetic animals were treated with *Carthamus tinctorius* extract at doses of 200 and 300 mg/kg body weight. Extract were given orally for 30 days and the values for blood glucose levels were observed after 15th and 30th day of treatment. While insulin levels were checked at the end of the study. Animals were also observed for any gross toxicity during the study. Results revealed that *Carthamus tinctorius* exerted significant hypoglycemic effect at 200 mg/kg and 300mg/kg doses as compared to diabetic control group. Insulin levels were significantly increased in *Carthamus tinctorius* treated groups as compared to diabetic control [121]. The chemical components isolated from safflower seed (*Carthamus tinctorius* L.) were evaluated as α-glucosidase inhibitors. The compounds appeared as active α-glucosidase inhibitors were serotonin derivatives (e.g. N-p-coumaroyl serotonin and N-feruloyl serotonin). These compounds showed a potent inhibitory activity, the 50% inhibitory concentration values were calculated as 47.2 µm and 99.8 µm respectively, while that of the reference drugs acarbose and 1-deoxynojirimycin were estimated as 907.5 µm and 278.0 µm, respectively. Regarding the structure of the serotonin derivative, the existence of the hydroxyl group at 5-position in the serotonin moiety and the linkage of cinnamic acid and serotonin were essential for α-glucosidase inhibitory activities. The authors suggested that these results are helpful for the proper use of safflower seed as traditional medicine for the treatment of diabetes, moreover, it could serve to develop medicinal preparations as supplements and functional foods for diabetics [122].

Cassia occidentalis

The methanolic extract of *C. occidentalis* leaves was tested against alloxan-induced diabetic mice. The diabetes in the experimental mice was induced by a single intraperitoneal injection of alloxan. Treatment with *C. occidentalis* leaf extract at different doses (200 mg/kg, 300 mg/kg, and 450 mg/kg orally) significantly reduced the blood glucose level to normal in diabetic mice [123]. Methanol fraction of *C. occidentalis* leaves (COLMF) was tested against streptozotocin-induced diabetic rats. Oral administration of COLMF significantly and dose-dependently normalized hemoglobin, glycosylated hemoglobin, hepatic glycogen, lipid peroxidation, antioxidants (TBARS, HP, SOD, CAT, GPx VitC, VitE, GSH) and hepatic marker enzymes (ALT, AST, ALP, ACP) near to normal in STZ-diabetic rats ($p<0.05$). Histopathological examination showed that COLMF protected the pancreatic tissue from STZ-induced damage [124]. Aqueous extract of *C. occidentalis* produced a significant reduction in fasting blood glucose levels in the normal and alloxan-induced diabetic rats. Petroleum ether extract showed activity from day 14 and chloroform extract showed activity from day 7. Significant differences were observed in serum lipid profiles (cholesterol and triglyceride), serum protein, and changes in body weight by aqueous extract treated-diabetic animals, when compared with the diabetic control and normal animals. Concurrent histopathological studies of the pancreas of these animals showed comparable regeneration by extract which were earlier necrosed by alloxan [125]. Antidiabetic effect of the butanol (DTB) and aqueous (DTA) leaves extracts of *Cassia occidentalis* was evaluated in alloxan-induced diabetic mice. DTB group showed significant reduction in plasma glucose levels (95.2±7.46). DTA group showed significant reduction (119.6±29.03) but was less as compared with the DTB group. DTB group showed significant reduction in plasma cholesterol levels (186± 14.8). DTA group (190± 14.81) also showed significant reduction but slightly less as compared with the DTB group. DTB group showed significant reduction in LDL levels (99.7±7.3). Reduction in LDL levels in DTA group (111±5.1) was also significant as compared to DTB group. However, both extracts didn't induced significant changes in HDL and triglycerides levels [126].

Casuarina equisetifolia

The antidiabetic activity of *Casuarina equisetifolia* leaves ethanolic extract (EECE) was evaluated against streptozotocin (STZ) induced experimental rats. Blood glucose levels were determined on 0, 7th, 14th and 21st day after oral administration of ethanolic extracts of *Casuarina equisetifolia* (400mg/kg). An ethanolic extract of *C. equisetifolia* was found to reduce blood sugar in streptozotocin induced diabetic rats. Reduction in blood sugar could be seen from 7th day after continuous administration of the extract. The effect of extracts of *Casuarina equisetifolia* on serum lipid, total cholesterol, triglycerides, low density and high density lipoprotein were also measured in the diabetic and non diabetic rats. There was significant reduction in total cholesterol, LDL cholesterol, VLDL cholesterol and improvement in HDL cholesterol in diabetic rats [127]. The effect of *Casuarina equisetifolia* bark incorporated into rat feed at 10-40% on the lipid profiles and blood sugar of albino rats was investigated. The parameters studied were triacylglycerol (TGL), total cholesterol (TC), total lipid (TL), phospholipids (PHOS), high-density lipoprotein (HDL) and random blood sugar (RBS). There was no significant change ($P>0.05$) in the TGL levels of all the rats, including the control, as they all range between 0.18-0.22(mg/dl). The effects on TC and TL were irregular as they did not display any dose dependence. The mean plasma PHOS levels did not change significantly ($P>0.05$) between the control and the rats fed on 10% feed (0.19± 0.00 vs 0.18± 0.00 mg/dl), but was significantly lowered ($P<0.05$) at 20-40% feed

content. The mean HDL level rose, although insignificantly (P>0.05) with the percentage contents of the bark in the feeds; by implication, the low-density lipoprotein (LDL) was decreasing with the increase in the bark contents of the feeds. The RBS also decreased as the percentage bark contents of the feeds increased, indication that it could have anti-diabetic properties [128].

CONCLUSION

The paper reviewed the antidiabetic effects of the medicinal plants to open the door for their utilization in medical applications as a result of effectiveness and safety**.**

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