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Systematic Review

Medicinal Plants: Role in treatment of Diabetes

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Abstract

Diabetes is one the world's most widespread diseases, affecting over 327 million people and causing about 300,000 deaths annually. Despite great advances in prevention and therapy, existing treatments for this disorder have serious side effects. Plants used in traditional medicine represent a valuable source in the search for new medicinal compounds.

1. Introduction

Diabetes Mellitus (DM) is an endocrinological disorder and is a group of metabolic or heterogeneous afflictions resulting from an irregularity in insulin secretion and insulin action or both. Absent or reduced insulin levels lead to persistent abnormally high blood sugar and glucose intolerance[1]. Diabetes mellitus affects at least 5.6% of the global population[2,3], and it is predicated that by 2040, 642 million people will be living with diabetes[2]. In terms of mortality, the WHO has reported that in 2012 directly caused 1.5 million deaths, and an additional 2.2 million deaths were attributed to high blood glucose concentrations and the associated increased risk of disease[4-6].

India is known as diabetes capical of world. Kaveeshwar and Cornwall (2014) reported that there are 62 million individuals are diagnosed with diabetes which is fast gaining the status of a potential epidemic in India. In 2000, India (31.7 million) topped the word with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively[7]. Kokiwar *et al*. 2010 studied the prevalence of diabetes in rural area of central India and concluded that there was high prevalence of diabetes (3.67%) as compared to that in the WHO report (2.4%) for rural India[8].

The prolonged condition of hyperglycemia and hyperlipidemia increases the onset of diabetes and reports suggest that chronic hyperglycemia could be a cause of insulin resistance. Furthermore, these elevated levels of sugar, non-enzymatically glycate the different biomolecules (protein or Lipid) which disrupt normal functioning of cells/tissues and organ systems[9].

There are several glucose-lowering synthetic drugs are available that exert anti-diabetic effects through different mechanisms. These mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones[10], delay in the absorption of carbohydrates from the intestine by alpha-glucosidase, and reduction of hepatic gluconeogenesis by biguanides[11,12]. There are various side effects has been reported of synthetic medicines and their interactions with each other in vitro must be considered by medical staff[12,13]. In the past three decades, despite the significant progress made in the treatment of diabetes, the results of treatment in patients is still far from perfect. Today, many treatments that involve the use of medicinal plants are recommended by physicians in many developed and developing country[14-16].

Plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and have anti diabetic effects[16,17]. The anti-hyperglycemic impacts that outcomes from treatment with plants are frequently due to their capacity to improve the execution of pancreatic tissue, which is finished by expanding insulin emissions or diminishing the intestinal retention of glucose. The quantity of individuals with diabetes today has been developing and causing expanding worries in medicinal network and people in general. The principle reason for this article is to present a number of viable therapeutic plants utilized for treating diabetes and different components of plant mixes used to decrease glucose levels and increment insulin secretion.

2. Materials and Methods

Materials

Publication regarding diabetes and effective plants were extracted in databases such as Nature, Science Direct, Google Scholar, PubMed, ResearchGate, Wiley, Scopus, and Springer. Keywords used in this study included "Anti diabetic Plants", "diabetes", "Diabetic Complications ", and "treatment". Out of the 4285 collected articles (published in the period between 2015 and 2019), 3780 were excluded due to non-relevance or lack of access to the original article.

Inclusion and exclusion criteria

The search was restricted to English language articles. All studies found during the search were independently evaluated for competence and inclusion by two different authors. After compliance with inclusion criteria, experimental research and clinical trials that evaluate the effect of medicinal herbs or plant component in diabetic animals or patients were included in the current research. Irrelevant studies or original article that evaluated mixed plant extract, algae, or mushroom extracts were also excluded.

3. Results and discussion

Antidesma bunius

In a study it was revealed that leaves of *Antidesma bunius* plant have the potential inhibitory effect of α-amylase and α-glucosidase activity in comparison to acarbose[18]. The methenolic extract (250 mg/kg body weight) of *Antidesma bunius* leaves was given orally to alloxan-induced diabetic rats for 28 days. Blood glucose, insulin, TC, TG, amylase, lipase, liver glycogen were analysed. The extract revealed a significant reduction in blood glucose level (80.5%) along with an increase in serum insulin (134%), lipase (90.7%) and liver glycogen level (160%). Also amylase (28.2%) activity, TC (40.2%), and TG (28.8%) levels were significantly decreased when compared with diabetic control rats. A. bunius extract improved the histo-architectural of the β-cells[19].

Gynostemma pentaphyllum

From Gynostemma pentaphyllum a polysaccharide was isolated and orally administered 0.5 ml (1mg/ml) to the diabetic mice for 30 days. The Fasting blood sugar of diabetic mice decreased from 17.56 mmol/L to 7.42 mmol/L[20]. The anti diabetic effect of Gynostemma pentaphyllum was studied to investigate the mechanisms of insulin release in Goto-Kakizaki (GK) rat, an animal model of type 2 diabetes and revealed that an oral treatment with GP (0.3 g/kg of body weight daily) for two weeks in GK rats improved glucose tolerance versus placebo group ($P<0.3$ g/Kg of body weight daily) for two weeks in GK rats improved glucose tolerance versus placebo group ($P<0.01$) Plasma insulin levels were significantly increased in the GP-treated group. The insulin release from GP-treated GK rats was 1.9-fold higher as compared to the control group ($P<0.001$). GP stimulated insulin release in isolated GK rat islets at high glucose. Opening of ATP-sensitive potassium (K-ATP) channels by diazoxide and inhibition of calcium channels by nifedipine significantly decreased insulin response to GP. Furthermore, the protein kinase A (PKA) inhibitor H89 decreased the insulin response to GP ($P<0.05$) In addition, GP-induced insulin secretion was decreased after preincubation of GK islets with pertussis toxin to inhibit exocytotic Ge proteins ($P<0.05$)[21].

Rhinacanthus nasutu

Rhinacanthus nasutu has traditionally been used to cure various type of disease including diabetesmellitus. A study, investigating on the antihyperglycemic and anti-hyperlipidemic activity reveals that RRE (15 mg/kg equivalent to Rhinacanthins content) in comparison to its marker compound RC (15 mg/kg) and the standard drug glibenclamide (Glb) (600 µg/kg) in nicotinamide streptozotocin induced diabetic rats for 28 days. In addition, the *in silico* pharmacokinetic and toxicity analysis of RC was also performed. RRE, RC and Glb significantly reduced the FBG, HbA1c and food/water intake while increasing the insulin level and body weight in diabetic rats without affecting the normal rats. The serum lipid, liver and kidney biomarkers were markedly normalized by RRE, RC and Glb in diabetic rats without affecting the normal rats. Moreover, the histopathology of the pancreas revealed that RRE, RC and Glb evidently restored the islets of Langerhans in diabetic rats[22]. A alloxan induced diabetic test model were performed to evaluate antidiabetic activity of extract of Rhinacanthus nasutus (ERN) at two different doses 200 and 400 mg/kg respectively. Ethanolic extract of Rhinacanthus nasutus leaves (Acanthaceae) was tested for anti-diabetic activity for alloxan induced diabetics in wistar rats. After oral administration of the extract at two different doses (200 and 400mg/kg body weight) for 21 days to alloxan induced diabetic rats, the blood glucose, level was assayed periodically on 0, 7, 14 and 21th day. After 21 days treatment all biochemical parameters like total cholesterol, triglyceride, total protein levels were checked and compare with control and standard group and body weight was

also determine which was compare with initial weight the result reveals that there was significant control of all biochemical parameters levels like total cholesterol, triglyceride, total protein in extracts of Rhinacanthus nasutus leaves treated diabetic rats. Marked body weight loss was observed in diabetic rats. The data obtained from this study showed that the treatment of extracts Rhinacanthus nasutus leaves protect the diabetic rats from loss of massive body[23].

Cyclocarya paliurus

Cyclocarya paliurus, a native medicinal plant to China, has been widely used as a traditional medicine in the treatment for diabetes. The polysaccharide extracted from the leaves of Cyclocarya paliurus was studied for antidiabetic activity and results from this study demonstrated CPP (Cyclocarya paliurus polysaccharides) could protect pancreas islets through decreasing oxidative stress and pro-inflammatory cytokines, and alleviate dyslipidemia, hepatic steatosis and liver injury. Pancreatic transcriptome profiling suggested CPP could down-regulate genes related to mitochondrion and fatty acid metabolism process, which decreased the production of reactive oxygen species and alleviated oxidative stress damage. Besides, liver transcriptome analysis indicated CPP down-regulated biological processes related to lipid metabolic, oxidation-reduction and apoptosis, and up-regulated protein synthesis, which contributed to preventing liver injuries[24]. In other study the *C. paliurus* leaves with different chemical compositions were selected from five geographical locations, and their effects on streptozotocin (STZ)-induced diabetic mice were evaluated with both ethanol and aqueous extracts. Glucose levels, lipid levels, and biomarkers of liver and kidney function were measured and they suggested that the composition of *C. paliurus* compounds might help to design therapeutic alternatives for the treatment of diabetes mellitus[25].

Scutellaria baicalensis* and *Coptis chinensis

Scutellaria–coptis herb couple (SC) is one of the well-known herb couples in many traditional Chinese compound formulas used for the treatment of diabetes mellitus (DM), which has been used to treat DM for thousands of years in China. In a study Scutellaria–coptis (SC) significantly increased blood HDL and significantly reduced fasting blood glucose, fasting blood insulin, glycosylated hemoglobin, glycosylated serum protein, TC, TG, LPS, IL-6 and TNF-α levels ($P < 0.05$ or $P < 0.01$) in type-2 diabetic KK-Ay mice. Furthermore, SC could regulate the structure of intestinal flora. Additionally, the expressions of TLR4 and MyD88 protein in the colons were significantly decreased in the model group ($P < 0.05$ or $P < 0.01$). However, SC had no significant effect on weight gain. In RAW264.7 macrophages, SC containing serum (SC-CS) (5%, 10% and 20%) significantly decreased IL-6, TNF-α, TLR4 and MyD88 protein levels and the mRNA expression of IL-6, TNF-α and TLR4 ($P < 0.05$ or $P < 0.01$)[26]. In another reserarch a rapid, reliable and automated analysis method, ultra-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry (UPLC-Q-TOF/MS) technique, combined with Metabolynx™ software, was applied for the identification of the metabolites of the main bioactive components in scutellaria–coptis extract by intestinal bacteria from normal and type 2 diabetic rat feces. The data obtained from above work reveals that type 2 diabetic rat intestinal flora could generate a great number of baicalein (M2), the aglycone of baicalin, compared with normal samples. In addition, the intestinal flora of normal rats could also produce several conjugates such as hydrogenated baicalin (M1), sulfated berberine (M4), and glucuronidated berberine (M5), while the intestinal flora derived from type 2 diabetic rats could engender oroxylin A (M3) and methylated berberine (M6)[27].

Pueraria lobata

P. lobata exhibited high PTP1B inhibitory activity with IC_{50} of 0.043 mg/ml. Treated insulin-resistant HepG2 cells with 0.0115 mg/ml of *P. lobata* increased the glucose uptake by two times compared with the negative control. Further, we performed OGTT test on the diabetic C57BL/6 male mice. 20% decreased blood glucose (AUC) was obtained with a dose of 1 g/kg *P. Lobata* compared with the negative control. Herein, we were able to demonstrate the antidiabetic effects of *P. lobata* might be related to the inhibition of PTP1B and therefore, bettering the insulin signaling pathway[28]. Puerarin effectively alleviated dyslipidemia and decreased the accumulation of intramyocellular lipids by upregulating the expression of a range of genes involved in mitochondrial biogenesis, oxidative phosphorylation, the detoxification of reactive oxygen species, and the oxidation of fatty acids in the muscle of diabetic rats. Also, the effect of puerarin on mitochondrial biogenesis might partially involve the function of the μ-opioid receptor. In addition, puerarin decreased the trafficking of fatty acid translocase/CD36 to the plasma membrane to reduce the uptake of fatty acids by myocytes. In vitro studies confirmed that puerarin acted directly on muscle cells to promote

the oxidation of fatty acids in insulin-resistant myotubes treated with palmitate[29].

Nerium oleander

Nerium oleander leaf extract (NOLE) demonstrated antihyperglycaemic activity by reducing 73.79% blood glucose level after 20 days of treatment. Oral glucose tolerance test (OGTT) revealed increase in glucose tolerance as evident by 65.72% decrease in blood glucose in 3 h post treatment. Percentage decrease in different liver marker enzymes were significant along with decrease in triglyceride and cholesterol levels, displaying potent antihyperlipidemic activity. Peroxidase and catalase activity in liver, kidney and skeletal muscle were significantly restored besides marked reduction in lipid peroxidation and normalization of hepatic glycogen level in the NOLE treated alloxanized mice. Different bioactive phytocompounds with potent anti-diabetic activity were identified by GC–MS and HPLC analysis[30]. Stem and roots of *N. oleander* were collected, dried and extracted by using well-established methods for alkaloids, flavonoids, steroids and crude extracts in polar and non-polar solvents. Evaluation of their antidiabetic activity using In Vitro alpha amylase inhibition method and found that highest inhibition for stem its free flavonoid extract at the concentration of 1.5 mg/ml, with percent inhibition 48.35±1.36 % and an IC50 value of 1.774 g/ml while in case of root, highest inhibition was obtained at 1.5 mg/ml of pet ether extract, with % inhibition 52±0.40 % and IC50 value 1.583 g/ml and at 1.5 mg/ml of methanol extract, with % inhibition 42.12±1.12 % and an IC50 value 1.729 g/ml. 8 (5 of stem and 3 of root) out of 14 tested extracts have shown good inhibitory potential. Extracts of the stem were found to be more potent than root extracts[31].

Cassia Siamea

The ethanolic extract and n-hexane fraction of *Cassia siamea* Lamk (Juar) leaves have anti-diabetic activity in Webster albino mice induced with alloxan. The extract of *Cassia siamea* Lamk leaves, the fractions of 500 mg ethyl acetate and 500 mg n-Hexana of *Cassia siamea* Lamk provided better performances in lowering blood glucose levels compared to Ethanol extracts both 500 mg and 1000 mg. In the form of ethyl acetate and n-hexane fraction at a dose of 150 mg/kg BW provided the highest anti-diabetic activity compared to the other test groups that are able to decrease blood sugar level by 10.25% and 9.98% respectively. Its effect is equivalent to glibenclamide at a dose of 0.65 mg/kg BW which can lower blood sugar levels by 9.27%. Thus *Cassia siamea* Lamk leaf is very potential as an alternative drug antidiabetes mellitus, and the 1000 mg Ethanol extract, 150 mg Ethyl acetate and 150 mg n-Hexana had no difference effects in lowering blood glucose levels compared to the anti-diabetic chemical drug glibenclamide[32]. In other study it is reported that Dose of 2000 mg/kg bw of aqueous extracts of C. siamea was not toxic. In non-diabetic rats, LACS significantly prevented oral glucose-induced hyperglycemia. In diabetic rats, this extract significantly increased the body weight without modifying the food intake after four weeks of administration. Interestingly, it significantly reversed the hyperglycemia and improved kidney functions, i.e reduced serum urea and creatinine levels without affecting the serum concentrations of Na^+, K^+, Cland $Ca2^{+33}$.

Momordica charantia

A water-soluble polysaccharide (MCP) was isolated from the fruits of *Momordica charantia* L., and the hypoglycemic effects of MCP were investigated in both normal healthy and alloxan-induced diabetic mice. MCP was orally administered once a day after 3 days of alloxan-induction at 100, 200 and 300 mg/kg body weight for 28 day. Results reveals that fasting blood glucose level (BGL) was significantly decreased, whereas the glucose tolerance was marked improvement in alloxan-induced diabetic mice, and loss in body weight was also prevented in diabetic mice compared to the diabetic control group. The dosage of 300 mg/kg body weight exhibited the best effects. In addition, MCP did not exhibit any toxic symptoms in the limited toxicity evaluation in mice[34]. In another study male Wister rats were randomly assigned to 4 groups. Group I, Normal control; Group II, STZ diabetic; Group III and IV, Momordica charantia fruit juice was orally administered to diabetic rats (10 mL/kg/day either as prophylaxis for 14 days before induction of diabetes then 21 days treatment, or as treatment given for 21 days after induction of diabetes). The effects of *charantia* (MC) juice were studied both in vivo and in vitro by studying the glucose uptake of isolated rat diaphragm muscles in the presence and absence of insulin. The result showed that that MC caused a significant reduction of serum glucose (135.99 ± 6.27 and 149.79 ± 1.90 vs. 253.40 ± 8.18) for prophylaxis and treatment respectively, fructosamine (0.99 ± 0.01 and 1.01 ± 0.04 vs. 3.04 ± 0.07), total cholesterol, triglycerides levels, insulin resistance index (1.13 ± 0.08 and 1.19 ± 0.05 vs. 1.48 ± 1.47) and pancreatic malondialdehyde content ($p < 0.05$). While it induced a significant increase of serum insulin (3.41 ± 0.08 and 3.28 ± 0.08 vs. 2.39 ± 0.27), HDL-cholesterol, total antioxidant

capacity levels, β cell function percent, and pancreatic reduced glutathione (GSH) content ($p < 0.05$) and improved histopathological changes of the pancreas. It also increased glucose uptake by diaphragms of normal (12.17 ± 0.60 vs. 9.07 ± 0.66) and diabetic rats (8.37 ± 0.28 vs. 4.29 ± 0.51) in the absence and presence of insulin ($p < 0.05$)[35].

Talinum triangulare

The anti-diabetic effects of the polysaccharides obtained from *Talinum triangulare* (TTP) was studied. Two TTP doses (150 mg/kg and 300 mg/kg·bw/d) were administered orally to normal and streptozotocin (STZ)-induced type 2 diabetic male Kunming mice, respectively. The TTP hypoglycemic and hypolipidemic effects were evaluated by testing the fast blood glucose (FBG) level, fasting serum insulin (FINS), and serum lipids (TC, TG, HDL, LDL) as well as the body, hepar and kidney weights. After four weeks administration, the low-dose group 150 mg/kg·bw/d) and high-dose group (300 mg/kg·bw/d) showed a marked FBG fall rate of 29.85% and 41.18% (FBG fall rate % = ((Diabetic control − TTP group)/Diabetic control) × 100%). The results of FBG and serum lipids indicate that TTP possess significant hypoglycemic effect, but no significant hypolipidemic effect. These results suggest the potential use of TTP as a functional food for the treatment of type 2 diabetic mellitus (T2DM)[36]. The Wistar rats (180-210g) divided into six groups of six animals (males) each were fed 2% cholesterol-enriched diet and orally treated with 0.9% saline or extract of Talinum triangulare (250, 500, and 1000 mg/kg per body weight) daily for eight weeks. Lipid profile, lipid peroxidation (MDA), hematological parameters, and their functional indices and serum antioxidant enzymes (catalase, glutathione -S-transferase, and superoxide dismutase) activities and glutathione status were assessed in normal and diet-induced hypercholesterolemic extract treated rats and compared with the rats treated with 100 mg/kg per bwt standard drug gemfibrozil. The result showed that A significant ($P < 0.05$) increase in lipid profile (total glyceride, total cholestrol, low-density lipoprotein, and very low-density lipoprotein), MDA and reduction ($P < 0.05$) in enzymatic and nonenzymatic antioxidant status coupled with alterations in hematological parameters was observed in the serum of hypercholesterolemic rats when compared with animals on a normal diet. Coadministration of methanolic leaf extracts of Talinum triangulare or gemfibrozil significantly ($P < 0.05$) restored the elevated serum lipid profile, MDA, and the deranged hematological parameters to near normal. The extract also protected against hypercholesterolemic-induced diminished enzymatic and nonenzymatic antioxidant status. The activities of the plant extract are dose (250, 500, and 1000 mg/kg) dependent and it compared favorably with the standard drug gemfibrozil[37].

Mentha piperita

Mentha pipperita infusions prepared from elicited plants (2 mM salicylic acid) increased their content of several compounds, principally *p*-hydroxybenzoic and rosmarinic acids, hesperidin, quercetin-3-O-glucoside, α-tocopherol, and β-sitosterol. The administration of these infusions decreased microalbumin and urea in urine and serum uric acid levels, and the renal accumulation of 14 inflammation-related proteins. These proteins were associated with glomerular hypertrophy, tubular damage, expansion of mesangial matrix, and cell death. The application of 2 mM SA during peppermint cultivation improved the renoprotective properties of peppermint infusions[38]. In a study it was evaluated that the hypoglycemic, hypocholesterolemic and antioxidant properties of Mentha spicata (Labiateae) leaves aqueous extract (MSLA) in alloxan-induced diabetic rats. Hyperglycemia was induced in male rats by intraperitoneal injection of alloxan monohydrate (150 mg/kg). The aqueous extract of M. spicata was orally administered at a dose of 300 mg/kg body weight to diabetic rats for 21 days and the effects were compared with glibenclamid (2 mg/kg). Fasing blood sugar (FBS), body weight, lipid profile and serum malondialdehyde (MDA) were monitored at 0, 7, 14 and 21 days after induction of diabetes. Total phenol contents (TP) and reducing power (RP) were also evaluated. TP and RP of aqueous extract were 2.763 ± 0.39 mg Galic acid/gr and 0.026 ± 0.001 EC50 mg/mL, respectively. The LD50 of the extract was found to be > 1500 mg/kg. The administration of M. spicata aqueous extract produced a significant reduction ($P<0.01$) in FBS, total cholesterol, triglyceride, low density lipoprotein-cholesterol and MDA (101.83 ± 4.33, 95.66 ± 4.75, 89.83 ± 5.26, 26.20 ± 5.10 mg/dl and 1.53 ± 0.61 µmol/l, respectively) in diabetic rats. These effects were comparable with the effects of standard antidiabetic drug (glibenclamide)[39].

Olea europaea

The olive (*Olea europaea* L.) has important pharmacological functions, including anti-inflammatory, antioxidant, and hypoglycemic activities. The result showed that a significant decrease in body weight was observed among diabetic animals treated with

ethanol and EEOL compared to the control group. Moreover, animals treated with EEOL showed an improvement in glucose levels and in levels of inflammatory and metabolic markers when compared to diabetic animals[40]. In the other study the levels of serum glucose, insulin, total protein, albumin, triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), creatine kinase (CK), lactate dehydrogenase (LDH) and malondialdehyde (MDA) were significantly increased, while the levels of high density lipoprotein cholesterol (HDL-C), superoxide dismutase, (SOD) glutathione (GSH) and catalase (CAT) were statistically decreased in diabetic rats of the second group. The levels of liver insulin receptor substrate 1 (IRS1) and insulin receptor A (IRA) were significantly declined in diabetic rats of the second group. The diabetic pancreatic sections from diabetic rats of the second group showed several histopathological changes. Administration of low and high doses of olive leaves extract improved the observed physiological, molecular and histopathological alterations[41].

Punica granatum

It was investigated the protective effects of methanolic extract of *Punica granatum* leaves (MPGL) in streptozotocin-induced diabetic nephropathy. Diabetic nephropathy has become a leading cause of end stage renal failure worldwide. *P. granatum*, due to its anti-diabetic, anti-inflammatory and antioxidant activities may retard the progression of diabetic nephropathy. In this study, diabetes was induced by a single injection of streptozotocin (STZ, 45 mg/kg, i.p.) in rats. STZ-diabetic rats were treated with oral doses of MPGL (100, 200 and 400 mg/kg) for 8 weeks. At the end of the experimental period, body and kidney weight and blood glucose levels were determined. Serum and urine parameters were investigated. Antioxidant enzymes and lipid peroxide levels were determined in the kidney along with histopathological examination of the same. MPGL significantly increased body weight, lowered blood glucose levels and ameliorated kidney hypertrophy index in the STZ-diabetic rats. The extract also decreased the levels of creatinine, blood urea nitrogen, total cholesterol, triglycerides, advanced glycation end products and albumin in serum and urine, respectively. MPGL significantly increased the antioxidant parameters in the kidney. Histological evaluation revealed that MPGL treated STZ-diabetic rats demonstrated reduced vacuolar degeneration of tubules; periodic acid Schiff base (PAS) positivity staining intensity in glomeruli and basement membrane thickening[42].

Streptozotocin induced diabetic Wister rats were used for another study the results reveals that Higher dose of fruit peel extract of *P. granatum* (PEPG) and glibenclamide significantly lowered blood glucose level from 7th day onwards however glibenclamide was found to be more effective. Leaves extract at higher dose and fruit extract at lower dose also significantly lowered blood glucose level from 14th day onwards. Leaves extract at lower dose also significantly lowered blood glucose level from 21st day onwards. Glibenclamide and higher dose of fruit PEPG extract significantly reduced the total cholesterol, triglyceride levels and significantly increased the high density lipoprotein cholesterol level. Glibenclamide followed by higher dose was found more effective in reducing plasma thiobarbituric acid reactive substances and increasing levels of antioxidant enzymes (superoxide dismutase and catalase). No toxicity was observed even when both extracts were administered at 10 times of higher dose used in this study and no significant changes were seen when it were used chronically[43].

Ocimum basilicum

Evaluated the role of glucose transporter-4 (GLUT4) in the anti-diabetic effects of methanol, hexane and dichloromethane extracts of the aerial parts of *Ocimum basilicum* (OB) and to analyze their phytochemical composition. Phytochemical analysis of the three extracts by GC/MS using the silylation derivatization technique revealed 53 compounds, 17 of them were found for the first time in OB. Cytotoxic and anti-diabetic properties of the extracts were evaluated using L6-GLUT4myc muscle cells stably expressing myc epitope at the exofacial loop (GLUT4). No cytotoxic effects were observed in treated cells up to 0.25 mg/ml extract as measured with MTT and LDH-leakage assays. GLUT4 translocation to the plasma membrane was elevated by 3.5 and 7 folds (−/+ insulin) after treatment with OB extracts for 20 h[44]. Antihyperglycemic effect of the extract was determined by its effects on α-amylase and α-glucosidase *in vitro*, while antidiabetic properties were studied in alloxan induced diabetic rats treated for 28 days with extract and compared to those treated with oral metformin (150 mg/kg). The treatment with 100 and 200 mg/kg extract significantly ($P < 0.05$) reduced fasting blood glucose concentration and slightly increased mean body weight in treated groups. Oral glucose tolerance was also significantly ($P < 0.05$, 0.001) improved in 100 and 400 mg/kg extract-treated groups. The extract caused a dose-dependent increase in liver glycogen content, while it decreased alanine transferase (18.9-30.56%) and aspartate transferase (6.48-34.3%) levels in a non-

dose-dependent manner. A dose of 100 mg/kg also reduced serum cholesterol and triglycerides by 19.3 and 39.54%, compared to a 2.6% reduction of cholesterol seen in the metformin-treated group. The extract was observed to produce significant ($P < 0.001$) concentration-dependent inhibition of α-glucosidase (35.71-100%) and also α-amylase (23.55-81.52%), with estimated inhibitory concentration values of 1.62 and 3.86 mg/mL, respectively[45].

Bauhinia Variegata

Ethanolic extract of *B. Variegate* was administered orally to Streptozotocin (STZ) induced diabetic rats once daily for 21 days. Blood glucose levels were estimated at day 0, 7, 14 and 21 by glucometer (one touch) and lipid profile and histopathological examination of isolated organs (kidney, liver and pancreas) were also estimated on 21 day. The anti-oxidant activity of *B. variegata* was evaluated by performing 1,1-diphenylpicrylhydrazyl (DPPH) and hydrogen peroxide scavenging (H_2O_2) assays. *B. variegata* flower extract showed reduction in blood glucose level (90.00 mg/dL) at highest dose 400 mg/kg when compared with diabetic control rats (224.50 mg/dL). The levels of triglycerides, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) were restored while administrating *B. variegata*. In addition, the percentage inhibition of *B. variegata* was 86.60% and 68.47% at 100 µg/ml for DPPH and H_2O_2 radicals, respectively, which was near to standard BHT i.e. 91.63% (DPPH) and 73.42% (H_2O_2). It can be concluded from the present study that *B. variegata* possesses significant antidiabetic, *anti*-hyperlipidemic and antioxidant activities[46]. Bauhinia variegata commonly known as kachnar tree and is cultivated throughout India. The antidiabetic activity of ethanol extract of leaf of Bauhinia variegata extract was evaluated using albino wister rat i.e. alloxan induced diabetes in albino wister rat by glucometer method, with 50 mg/kg,100 mg/kg and 200 mg/kg and higher doses showed significant value[47].

Centella asiatica

Diabetic rats were orally treated with vehicle, *Centella asiatica* (CA) (500 and 1000 mg/kg) or metformin (300 mg/kg) daily for 14 days. Skeletal muscle activities of hexokinase (HK), phosphofructokinase (PFK) and fructose 1,6-bisphosphatase (FBPase) were determined by spectrophotometric assays while those of glycogen synthase (GS) and glycogen phosphorylase (GP) were assayed radio-chemically. The results reduced activities of HK (25%), PFK (88%), and GS (38%) when compared to non-diabetic rats. Treatment of diabetic rats with CA500 increased the activities of PFK (7-fold), and FBPase (23%). Further, treatment of diabetic rats with CA1000 also increased the activities of GS (27%) and GP (50%) with little change in these parameters for diabetic rats treated with CA500. These effects probably led to the reduced blood glucose level and elevated skeletal muscle glycogen content observed in CA-treated rats relative to diabetic controls. Furthermore, *Centella asiatica* (CA) treated rats had reduced the morphological damage of skeletal muscle fibres compared to the non-treated diabetic control rats[48]. The glucose and cholesterol lowering effect of the aqueous extract of *Centella asiatica* leaf using the alloxan-induced diabetic rats and compared the activity with diabetic control and antidiabetic drug (Glibenclamide). Leaf extract (50 mg/kg) of *C. asiatica* and Glibenclamide were administered to normal and experimental diabetic rats for the duration of 10 days. In the alloxan-induced diabetic rat model, *C. asiatica* extract (50 mg/kg) significantly ($p < 0.05$) lowered the fasting blood glucose level as well as the total cholesterol level. Serum insulin levels were not stimulated in the animals treated with the extract. In addition, changes in body weight, serum lipid profiles and liver glycogen levels assessed in the extract treated diabetic rats were compared with diabetic control and normal animals. Significant results ($p < 0.05$) were observed in the estimated parameters. Surprisingly, body weight was increased significantly ($p < 0.05$) in the *C. asiatica* treated diabetic group. Phytochemical screening showed the presence of alkaloids, flavonoids, glycosides, steroids and tannins in significant amounts[49].

Mangifera indica

Determined the nutraceutical composition of mango by-product (BP) and to evaluate the mechanisms related to its antidiabetic properties. Mango BP reduced ($p < 0.05$) serum glucose in streptozotocin-induced diabetic rats, which was not associated with a decreased glucose intestinal absorption or to the protection of Langerhans islets. Mango BP showed insulin mimetic effects in 3T3-L1 adipocyte cells, increasing Glut4, Irs1 and Pi3k expression. Mango BP reduced ($p < 0.05$) serum triacylglycerides in diabetic rats, which was associated to a decreased lipid intestinal absorption, and ameliorated diabetic nephropathy due to its renal antioxidant activity. The anti-diabetic effect of mango BP was associated to its high content of soluble fiber, as well as several polyphenols and carotenoids, like ellagic acid, gallic acid, quercetin, epicatechin gallate, and β-carotene[50]. Evaluated the antidiabetic and anticancer activities of the

ethanolic leaf extract of *Mangifera indica* cv. Okrong and its active phytochemical compound, mangiferin. Antidiabetic activities against yeast α-glucosidase and rat intestinal α-glucosidase were determined using 1 mM of p-nitro phenyl-α-D-glucopyranoside as substrate. Inhibitory activity against porcine pancreatic α-amylase was performed using 1 mM of 2-chloro-4 nitrophenol-α-D-maltotroside-3 as substrate. Nitrophenol product was spectrophotometrically measured at 405 nm. Anticancer activity was evaluated against five human cancer cell lines compared to two human normal cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Mango leaf extract and mangiferin exhibited dose-dependent inhibition against yeast α-glucosidase with the IC_{50} of 0.0503 and 0.5813 mg/ml, respectively, against rat α-glucosidase with the IC_{50} of 1.4528 and 0.4333 mg/ml, respectively, compared to acarbose with the IC_{50} of 11.9285 and 0.4493 mg/ml, respectively. For anticancer activity, mango leaf extract, at ≥200 µg/ml showed cytotoxic potential against all tested cancer cell lines[51].

Phoenix dactylifera

The effectiveness of hydroalcoholic extract of *Phoenix dactylifera* L. leaves (HEPdL) in animal models of type II diabetes *in vitro*/*in vivo* and in a human melanoma-derived cell line (IGR-39). A liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis was also performed to determine the amount of phenolic and flavonoid compounds in this plant. The physicochemical results by LC–MS/MS analysis of HEPdL showed the presence of 10 phenolic compounds. The *in vitro* study showed that the extract exhibited a more specific and potent inhibitor of α-glucosidase than α-amylase with an IC_{50} value of 20 ± 1 µg/mL and 30 ± 0.8 µg/mL, respectively. More importantly, the *in vivo* study of the postprandial hyperglycemia activity with (20 mg/kg) of HEPdL showed a decrease in plasma glucose levels after 60 min in resemblance to the glucor(acarbose) (50 mg/kg) effect. The oral administration of HEPdL (20 mg/kg) in alloxan-induced diabetic mices for 28 days showed a more significant anti-diabetic activity than that of the drug (50 mg/kg). Moreover, cytotoxicity effects of HEPdL in IGR-39 cancer cell lines were tested by MTT assay. This extract was effective in inhibiting cancer cells growth (IGR-39) at dose 35 and 75 µg/mL[52]. Total of seven groups of rats, consisting of control rats and streptozotocin induced diabetic rats treated with aqueous seed extract in concentration of 100g/L in dosage of 10ml/day/rat. To evaluate the anti-diabetic property, glucose and weight was analysed weekly and at the end of eight week all rats were sacrificed. To evaluate the hypolipidaemic and antioxidative activities, serum cholesterol, triglyceride, malondialdehyde, superoxide dismutase, 8-hydroxy-2'-deoxyguanosine were estimated. Liver enzymes and kidney function tests were performed. The aqueous seed extract of dates in concentration of 100 gm/L in dosage of 10ml/day/rat brings a significant reduction of blood glucose levels in diabetic rats in comparison of control rats. There were significant differences in the investigated clinical chemistry and oxidative stress parameters between control and diabetic rats with both seed extract of Ajwa and Sukkari dates[53].

Capparis spinosa

the nutraceutical potential of *Capparis spinosa* L. for the treatment of hyperglycemic states has been thoroughly investigated. A series of *in vivo* and *in vitro* tests have been conducted on fresh leaf, buds and salty buds (24 h desalted) processed to dry powder. 60% MeOH/H_2O extracts were obtained for HPLC analysis and for α-amylase and α-glucosidase inhibition tests. To estimate the *in vivo* anti-diabetic effect, dry powders of *C. spinosa* leaf and buds were orally administered to streptozocin-induced diabetic rats over a period of 28 days. At the end of the experiment, animals were sacrificed, blood taken for assessment of lipid profile and liver/kidney biochemistry while section of the pancreas, liver and kidneys were processed for general histology. Results showed that the regular administration of *C. spinosa* leaf or buds normalized all the biochemical parameters and reversed the liver/kidney injury with variable degrees of organ protection[54]. Rats were divided into six groups: normal control (NC), diabetic control (DC), diabetic rats receiving 0.2, 0.4 g/kg of plant extract or 0.6 mg/kg glibenclamide (groups D0.2, D0.4 or DG respectively). A normal group of rats was also designed to receive 0.2 g/kg of plant extract. Rats were rendered diabetic (streptozotocin 60 mg/kg, i.p.) and treated with 0.2, 0.4 g/ kg of plant extract or glibenclamide for four weeks. At the end of the experiment, blood was drawn through heart puncture under deep anesthesia. Weight was measured weekly, glucose levels were measured at the first and fourth week and lipid profiles, insulin and liver enzymes and the glucose levels significantly decreased after treating with plant extract (p=0.003). However, insulin levels did not increase in any treating groups. Plant extract could

significantly raise HDL and reduce levels of LDL and liver enzymes (ALT and ALP)[55].

Memecylon umbellatum

Evaluated the anti-diabetic and anti-obesity activity of methanolic extract of *Memecylon umbellatum* (MU) in alleviation of insulin resistance (IR). Diet induced obese (DIO) mice model was developed by feeding the mice on high fat diet (HFD) for 10 weeks resulting in hyperglycemia, obesity and IR. 250 mg/kg body weight of extract was administered orally daily for 8 weeks. Fasting glucose and body weight were monitored throughout the experiment. At the end of the study, serum parameters, histological examinations and gene expression pattern were analyzed. There was a significant reduction in fasting glucose levels, body weight and triglycerides. Improvement in the glucose tolerance and amelioration of insulin resistance was observed as revealed by reduction in serum IL6, serum oxidised LDL, histological sections of liver and subcutaneous adipose. Gene expression studies demonstrated the anti-inflammatory activity of the extract by down regulating IL6, PAI1 and ApoB gene expression as compared to the untreated HFD control. Our results demonstrate for the first time that oral administration of methanolic extract of MU in DIO mice leads to reduction in hyperglycemia, body weight, triglycerides and ameliorates insulin resistance[56]. alpha glucosidase inhibitory effect of isolated bioactive compound of Memecylon umbellatum. The isolated bioactive compound screened for α-glucosidase inhibitory activity using yeast glucosidase[57].

Hyptis verticillata

Results revealed that *H. verticillata* significantly lowered blood glucose level, attenuated dyslipidaemia, decreased atherogenic coefficient, atherogenic and coronary risk indices, and increased cardioprotective index in diabetic rats. Also, *H. verticillata* significantly decreased serum urea, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and unconjugated bilirubin levels, relative to untreated diabetic rats. Further, *H. verticillata* increased serum superoxide dismutase, catalase and glutathione peroxidase activities and glutathione level, and decreased malondialdehydelevel in diabetic rats in a manner similar to metformin and quercetin. Histopathological investigation of the liver and kidney revealed restored hepatocytes and amelioration of congested interstitial blood vessel of the Bowman's space of the kidneys upon intervention with *H. Verticillata*[58]. The paucity of information on the anti-hyperglycaemic potential of this plant, the present study assessed the anti-hyperglycaemic activity of H. verticillata leaf extract. Fifty-four albino Wistar rats were divided into two main groups consisting of diabetic and non-diabetic rats. The diabetic and non-diabetic rats were either treated with oral doses of metformin (500 mg/kg b.w.), quercetin (10 mg/kg b.w.), ethanol extract of H. verticillata leaf (low dose: 250 mg/kg b.w.) or H. verticillata (high dose: 500 mg/kg b.w.) for 28 days. Results showed significantly decreased body weight, increased fasting blood glucose (FBG) and glycated haemoglobin (HbA1c) levels, decreased pancreatic islet area and β-cell number in the diabetic untreated group, relative to normal control. H. verticillata - treated diabetic rats showed decreased FBG and HbA1c, increased body weight, pancreatic islet area and β-cell number, comparable to the effects of metformin[59].

Plantago asiatica

The effects of polysaccharide from *Plantago asiatica* L. (PLP) on high-fat diet and streptozotocin-induced type 2 diabetic rats were examined. Administration of PLP caused significant decreases in the concentrations of blood glucose, insulin, total cholesterol, triglyceride, non-esterified fatty acid and maleic dialdehyde, and significant increases in the levels of high density lipoprotein-cholesterol and the activities of antioxidant enzymes compared with diabetic rats after 4 weeks' treatment. The concentrations of short-chain fatty acids (SCFA) were significantly higher in the feces of diabetic rats after treatment with PLP. Moreover, colon bacterial diversity and abundance of bacteria, including Bacteroides vulgatus, *Lactobacillus* fermentum, *Prevotella loescheii* and *Bacteroides vulgates* were significantly increased by PLP treatment[60]. the therapeutic effects and underlying mechanisms of *Plantago asiatica* L. seed extract (PSE) on obesity and associated metabolic disorders in high-fat (HF) diet-induced mice. Our results displayed that PSE did not modify food intake or body weight but decreased abdominal white adipose tissue ratio, white/brown adipocyte size, serum total cholesterol, triglyceride (TG), low density lipoprotein cholesterol, free fatty acid, and hepatic TG concentrations when compared with the HF group. The levels of fasting blood glucose and glucose tolerance were improved in the PSE group when compared with the HF group. Furthermore, PSE upregulated mRNA expressions of peroxisome proliferator activated receptors (PPARs) and target genes related to fatty acid metabolism and energy

expenditure in liver and adipose tissue of obese mice when compared with the HF group[61].

Conclusion

Plants are natural antioxidants and effective herbal medicines, in part due to their anti-diabetic compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose. More researches are needed in order to separate the active components of plants and molecular interactions of their compounds for analysis of their curative properties.

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