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ANTIDIABETIC ACTIVITY OF SOME MEDICINAL PLANTS - A REVIEW

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ABSTRACT

In the last few years, there has been an exponential growth in the field of herbal medicine and gaining popularity both in developing and developed countries because of their natural origin and less side effects. A comprehensive review was conducted to pile up information about medicinal plants used for the treatment of diabetes mellitus. It is a metabolic disorder of the endocrine system and affecting nearly 10% of the population all over the world also the number of those affected is increasing day by day. The profiles presented include information about the scientific and family name, plant parts and test model used.

Keywords:

INTRODUCTION

Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of population in the World.[1] Diabetes mellitus is not a single disorder but it is a group of metabolic disorder characterised by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat, and protein metabolism. When ketones body is present in the blood or urine, it is called ketoacidosis, hence proper treatment should be taken immediately, else it can leads to other diabetic complications [2]. Diabetes mellitus has caused significant morbidity and mortality due to microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (heart attack, stroke and peripheral vascular disease) complications[3]. Diabetes is mainly attributed to the rapid rise in unhealthy life style, urbanization and aging. Hyperglycaemia which is the main symptom of diabetes mellitus generates reactive oxygen species (ROS) which cause lipid peroxidation and membrane damage. ROS plays an important role in the development of secondary complications in diabetes mellitus such as cataract, neuropathy and nephropathy. Antioxidants protect beta-cells from oxidation by inhibiting the peroxidation chain reaction and thus they play an important role in the diabetes. Plants containing natural antioxidants such as tannins, flavonoids, vitamin C and E can preserve beta-cell function and prevent diabetes induced ROS formation. Polyphenols, which are classified into many groups such as flavonoids, tannins and stilbenes, have been known as health-beneficial properties, which include free radical scavenging, inhibition of hydrolytic and oxidative enzymes, anti-inflammatory action and antidiabetogenic potentiality[4,5]. Aldose reductase as a key enzyme, catalyze the reduction of glucose to sorbitol and is associated in the chronic complications of diabetes such as peripheral neuropathy and retinopathy. Use of aldose reductase inhibitors and alpha-glucosidase inhibitors has been reported for the treatment of diabetic complications[6].

Pathophysiology of diabetes mellitus

Diabetes mellitus has a profound adverse effect on quality of life in terms of social, psychological well-being as well as physical health. Diabetic complications are mainly mediated through oxidative stress such as increased production of ROS or impaired antioxidant defense systems. Enhancement of lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism are the main factors involved in the development of diabetes [7]. Production of free radicals is also involved in the pathogenesis of various type of disease including diabetes mellitus [8]. Increased formation and accumulation of advanced glycation products (AGEs) is also involved in the diabetic complications, such as retinopathy, neuropathy, and renal dysfunction through a series of pathological changes [9]. Though several hormones are involved in the regulation of blood glucose level, the most important ones are insulin and glucagon.

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When imbalanced occurs in the level of hormones in the body, sugar starts accumulating in the blood and when concentration of glucone increased in the blood then finally it will passes in urine along with other minerals [10]. In most cases of diabetes, primarily T-cell mediates pancreatic islet beta-cell destruction, and becomes clinically symptomatic when 90% of pancreatic beta cells are destroyed. Serological markers such as islet cell, glutamic acid decarboxylase (GAD), IA-2, IA-beta, or insulin autoantibodies, are present in 85-90% of individuals when fasting hyperglycemia is detected. Sometimes environmental triggers, such as chemical or viral initiated pancreatic beta-cell destruction, which can triger consequences and thereby leads to the cause in diabetes mellitus. From the study it was found that enterovirus infection is also associated with the development of diabetes mellitus [11].

***Acacia arabica* bark (Leguminosae)**

Mechanism of action: Release of insulin from pancrease

Acacia Arabica has been studied for its hypoglycemic effect. Different parts of the plant with different extraction methods have been studied[12]. Although Acacia arabica was suggested as a hypoglycemic agent, very few studies measured its effect on insulin. This study was conducted to examine the effect of Acacia arabica bark extract on insulin, insulin resistance, Co-Q10, glucose, and lipid profile in streptozotocin (STZ)-induced diabetic rats. Hence, we can evaluate its role in the management of diabetes.

***Agrimony eupatoria* Leaves (Rosaceae)**

Mechanism of action: Insulin releasing and insulin like activity

The animal experiment was approved by the Ethical Committee of Faculty of Pharmacy, Comenius University in Bratislava (no. 962/10-221). Twenty-four male Wistar rats (DobráVoda, Slovak Republic) weighing 278g were used in the experiment. After a brief acclimatization period, rats were randomly divided into 4 groups (6 rats per group): (1) healthy animals-control group; (2) untreated diabetic group (DM was induced by i.p. (intraperitoneal) administration of STZ (Sigma-Aldrich) diluted in citrate buffer (pH 4.5) at a dose of 55 mg/kg); (3) and (4) diabetic animals daily treated for 5 weeks with tested plant extracts. Prior STZ administration blood glucose levels and total body weight of all animals were measured. The blood glucose levels and body weight were subsequently measured 1 and 5 weeks after DM induction. Following a 5-week period, all rats were killed by anesthetic overdose (thiopental, 100 mg/kg i.p., Sigma-Aldrich). Thoracic aortas and livers were immediately removed, repeatedly rinsed in saline, frozen in liquid nitrogen, and stored at 80oC until the analysis [13].

***Aloe barbadensis* latex (Liliaceae)**

Mechanism of action: Stimulating synthesis and release of insulin

Healthy male Swiss albino mice (weighing 20-30 g and age of 8-12 weeks) were purchased from Ethiopian Health and Nutrition Research Institute (EHNRI), Addis Ababa, and kept at the animal breeding house of Department of Pharmacology, University of Gondar. The animals were kept in polypropylene cage (6-10 animals per cage), under standard laboratory conditions (at room temperature, and with a 12 h light-dark cycle), and allowed free access to the standard pelleted diet and water ad libitum. Before the initiation of the experiment, the animals were acclimatized to the laboratory conditions for seven days. All experiments were performed according to animal care and welfare guidelines. Te experiment protocol was approved by the ethical review committee of the School of Pharmacy, University of Gondar. Finally, at the end of the experiment period animals were sacrificed by cervical dislocation.

Swiss albino male mice were used in this study based on previously published reports which revealed that female mice were less sensitive to STZ than males and were also associated with diminished survival rate due to severe induction of diabetes by STZ [14]. Animals were divided randomly into control and treatment groups which comprise six mice in each group. The negative control group received vehicle only, the positive control group received a standard drug glibenclamide 5mg/kg, and the remaining treatment groups were treated with three diferent doses (100, 200, and 400 mg/kg) of leaf latex extract. The doses of the extract were determined based on acute oral toxicity study. The middle dose 200mg/kg is one-tenth of the limit dose (2000 mg/kg), the higher dose 400 mg/kg is twice the middle dose, and the lower dose 100mg/kg was calculated as half of the middle dose. Glibenclamide 5 mg/kg was selected based on earlier studies [15,16]. The blood sample was collected from the tail vein of mice. Fasting blood glucose level (BGL) was determined using a glucometer and each sample was measured in triplicate and then averaged [17].

***Bixa orellana* (Bixaceae)**

Mechanism of action: Increase insulin concentration and increase insulin binding on insulin receptor

Male Wistar rats were kept under aseptic conditions in cycles of 12/12 hours light/darkness, at a temperature of approximately 221^{o}C. They were fed standard rat chow (Labinas, Brazil) and water ad libitum. The project submitted to and gained approval by the Institutional Committee of Ethics in Research. Diabetes mellitus was induced through the intraperitoneal injection of streptozotocin (SZT – SIGMA), in a single dose of 60mg/kg body weight, diluted in a citrate buffer, after anesthesia with sodium thiopental. The animals were divided into three experimental groups, with eight animals per group In a preliminary experiment the dose of 540 mg/kg was found to be the maximum dose that rats would tolerate without growth stunting or deterioration of their general condition. All animals had free access to tap water and standard chow (0.5% Na, 22% protein). None of the animals was treated with insulin throughout the entire

period of study. During the twelve-day-long experiment, we performed daily measurements of the animals body weight and blood sugar level (through a digital glucometer -One Touchs Ultrat/Lifescan). The experiment was divided in two phases. In this first phase, which lasted ten days, the animals treated with annatto received the drug between 4:00 and 5:00 P.M.; blood sugar levels were measured in the morning of the following day. In the second phase, on the eleventh day of treatment, annatto was administered in the morning and a blood glucose curb was drawn, with measurements of blood sugar level before drug administration (zero time), then at two, six and twelve hours after annatto ingestion. At 8:00 A.M. of the following day, blood glucose level was measured for the last time (12th day). Graph-Pad Prism (version 5.0) was used for the statistical analysis. The results were presented with means ± standard deviation. The comparison between groups was made by analysis of variance (ANOVA). Values of p o 0.05 were considered statistically significant [18].

***Boerhaavia Diffusa* Leaves (Nyctaginaceae)**

Mechanism of action: Increase plasma insulin concentration

In the experiment a total of 30 Albino Wistar rats (18 diabetic surviv-ing rats, 12 normal rats) were used. The rats were divided into five groups after the induction of Alloxan diabetes. In the experiment six rats were used in each group: Group 1,normal untreated rats; Group 2, normal rats given BLEt (200mg/kg of body weight in aqueous solution) daily using an intragastric tube for 4 weeks; Group 3, diabetic control rats; Group 4, diabetic rats given BLEt (200 mg/kg of bodyweight in aqueous solution) daily using an intragastric tube for 4 weeks13; and Group 5, diabetic rats give glibenclamide(600 g/kg of body weight in aqueous solution) daily usingan intragastric tube for 4 weeks [19]. At the end of 4 weeks, the animals were deprived of food overnight and sacrificed by decapitation. Blood was collected in tubes containing a potassium oxalate and sodium fluoride mixture for the estimation of blood glucose. Plasma was separated for the estimation of insulin and other bio-chemical parameters. Liver and kidney were dissected out, washed in ice cold saline, patted dry, and weighed [20,21].

***Camellia Sinensis* Leaves (Theaceae)**

Mechanism of action: Increase insulin secretion

The animals divided into six groups of four rats of each, consisting of three control groups and three treatment groups. Group I as standard control, healthy rats administered with daily oral of 0.5% carboxymethylcellulose (CMC). Group II as the negative control, diabetic rats administered with daily oral of 0.5% CMC. Group III as the positive control, diabetic rats administered with daily oral of 90 mg/kg sitagliptin. Group IV as lowest dose, diabetic rats administered with daily oral of 50 mg/kg white tea ethanolic extract (WTE). Group V as middle dose, diabetic rats administered with daily oral of 100 mg/kg WTE. Group VI as highest dose, diabetic rats administered with daily oral of 200 mg/kg WTE. The materials test administered at two days after induction of diabetic by injection of STZ for 14 days. Initial fasting blood glucose levels determined and after the induction fasting blood glucose were determined on the first day (D1) before the administration of the extracts and the 14th day (D14) after. Fasting blood glucose levels were determined by collecting the blood from the tail of the rats and measured using glucometer (Accu-Check® Active). Body weight of all animals was measured once before the treatment and twice after the treatment, on the 7th day (D7) and the 14th-day end of studies (D14). The fasting blood glucose levels of all treatment groups at the end of studies showed a significant difference between the negative control group, ($P < 0.05$) [22].

***Capsicum frutescens* fruits (Solanaceae)**

Mechanism of action: Increase insulin secretion and reduction of insulin binding on the insulin receptor

The experimental design was a full randomized block design with five treatments (R0, R5, R10, R15, and R20). Each lot of animals was randomly assigned to one of five diets. Foods used are: The food R0 (or control), which is floury provender contains 0% of C. frutescens; R5, R10, R15, and R20 are floury provender containing, respectively, 0.5%, 1%, 1.5%, and 2% of C. frutescens fruit powder. Each diet is supplemented by oil palm leaves ad libitum will. The data of this study suggest that 2% dietary C. frutescens are insulinotropic rather than hypoglycemic in the experimental methods[23,24].

***Cinnamomum Zeylanicum* Bark (Lauraceae)**

The rats were randomly divided into four groups. Group I: control animals (n=6) receiving the standard diet. Group II: alloxan-diabetic animals (n=6) receiving standard diet. Group III: control animals given standard diet with cinnamon (n=6). Group IV: alloxan-diabetic animals given standard diet with cinnamon (n=6). After 28 days, the animals were deprived of food overnight, sacrificed by decapitation, and then used in series of studies. Blood was collected from the jugular vein with heparin as anticoagulant and centrifuged at 1000 × g for 10 minutes to separate plasma (concerved at -20°C). Assays were carried in plasma for triglycerides, cholesterol, serum proteins and enzymes of oxidative stress.

The body was cut open, and then the pancreas was removed and washed in ice-cold saline (NaCl 0.9% at 2 ± 2°C). At a fraction of 0.4 g of pancreas, we added 4 mL of a solution of phosphate buffered saline (pH = 7.4), centrifuged at 3000 r/min for 30 min. The supernatant was collected and conserved at -80°C for further investigations [25].

***Eucalyptus Globulus* Leaves (Myrtaceae)**

Mechanism of action: Increase insulin secretion from clonal pancreatic beta line (BRIN-BD 11)

Fifty rats were divided into the five following groups (n = 10): (I) Control group (C): rats of this group receivedrodent diet and tap water. After one week theyreceived intraperitoneal vehicle (0.15 M NaCl with100 mM sodium citrate buffer).(II) Diabetic group (D): in this

group diabetes wasinduced by a single intraperitoneal injection ofstreptozotocin (60 mg/kg of body weight in 0.15 MNaCl with 100 mM sodium citrate buffer, pH 4.5).(III) Treated control group (TC): healthy rats receivedeucalyptus supplemented diet and drinking wa-ter. Eucalyptus was incorporated into the diet(62.5 g/kg) and drinking water (2.5 g/L) .(IV and V) Treated diabetic groups (TD1, 2): thesegroups received, respectively, 20 and 62.5 g/kgeucalyptus in the diet, and 2.5 g/L AEE in drink-ing water, from one week after induction of dia-betes by streptozotocin.The eucalyptus treatment began one week afterinduction of diabetes and lasted for four weeks, andthen the rats were killed. Food and fluid intake ofall groups were measured daily. Body weight andblood glucose were measured every week [26,27].

***Hibiscus Rosa* Leaves (Malvaceae)**

Mechanism of action: Stimulate insulin secretion from beta cells

Group 1 - control mice treated with vehicle alone. Group 2 - mice treated with insulin (1 ml of Biphasic isophane insulin purchased from pharmaceutical company dissolved in 100 ml saline and 0.1 ml/mouse/day was injected, (intraperitoneal). Group 3 - mice treated with F3 (100 mg/kg body weight). Group 4 - mice treated with F3 (200 mg/kg body weight). Group 5 - mice treated with F5 (100 mg/kg body weight). Group 6 - mice treated with F5 (200 mg/kg of body weight). F3 and F5 were dissolved in tween-80 (1%) and fed orally to the animals of group 3–6 as indicated. The experiment was conducted for four weeks. Serum glucose levels were estimated using a glucometer (EZ Omnitest) every week to ascertain the status of diabetes in different groups of mice. Similarly body weight was recorded once in a week in every group. After 30 days animals were allowed to fast overnight with free access to water and autopsied under light ether anesthesia. The blood was collected from the carotid artery at the time of autopsy and centrifuged at 4oC, at 10000 rpm for 10min; the separated serum was used for various biochemical analyses.

Serum glucose levels were estimated by Trinder's method using GOD POD enzymatic kit. Glycosylated haemoglobin, triglycerides, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol were estimated. Blood urea was estimated by urea-glutamate dehydrogenase (GLDH) method. Plasma insulin levels were determined in duplicate using insulin RIA Kit (Linco, St. Charles MO) with rat insulin as a standard. Data were statically evaluated by using one-way ANOVA. Wherever the ANOVA values were found to be significant Duncan's new multiple range test (DMRT) was applied (SPSS computer software). The values were considered significant when $P < 0.05$ [28].

***Ipomoea Batata* Roots (Convolvulaceae)**

Mechanism of action: Reduce insulin resistance and blood glucose level

Group 1: Normal control young animals; Group 2: Normal control old animals; Group 3: Diabetic control young animals; Group 4: Diabetic control old animals; Group 5: Methanol extract–treated young diabetic rats; and Group 6: Methanol extract–treated old diabetic rats.

Diabetic groups were given orally methanol extract with dose rate of 4 g/kg/day daily for 14 days on the basis of literature reviewed and primary dose optimization study having maximum antidiabetic effect. Feed usage and body weight of experimental rats were recorded before starting the dose and at 3rd, 6th, 9th, 12th, and 15th day of the experiment [29].

***Olea Europia* (Oleaceae)**

Mechanism of action: Increase insulin release and increase peripheral uptake of glucose

Experimental Animal Adult male albino rats were kept at 25 ± 2°C and 50–60% humidity, with 12 h light/dark cycle. Diabetic Induction Alloxan monohydrate (BDH Chemical Ltd. England) was used to induce diabetes as described by Antathan. Briefly, animals were injected with single subcutaneous injection of freshly prepared 100 mg /kg body weight of alloxan in 0.1M citrate buffer pH = 4.5. The control animals received citrate buffer only (Nimenibo-Vadia, 2003). Alloxan treated animals were allowed to drink 5% of D-Glucose (Merck KGG, a Darmstadt Germany) overnight to prevent the potentially fatal hypoglycaemia occurring as a result of massive insulin release following alloxan injection (Wohaeib and Godin, 1987). Diabetes mellitus was confirmed by testing blood glucose using indicator sticks (Accu-check Roche Diagnostics GmbH, Mannheim, Germany). After 3 days, the diabetes animals were detected based on loss of body weight, polyuria, glycosuria, polydipsia, polyphagia and blood glucose levels. Rats with blood Glucose level of ≥300 mg/dl were considered as diabetic and have been used in this study. In this experiment, the total of 48 rats (n = 8) were used and they were fed with standard diet and allowed to drink water ad libitum. The animals were grouped randomly into six groups as followings: Group I-Normal control: rats of this group received no induction and treatment. Group II-Diabetic control: diabetic rats of this group received no treatment. Group III- treated diabetic group: diabetic rats of this group received 5 mg/kg of body weight of pure oleuropein compound. Group IV- treated diabetic group: diabetic rats of this group received 10 mg/kg of body weight of pure oleuropein compound. Group V- treated diabetic group: diabetic rats of this group received 15 mg/kg of body weight of pure oleuropein compound. Group VI- treated diabetic group: diabetic rats of this group received 20 mg/kg of body weight of pure oleuropein compound. Following 40 days of treatment, prior the fasting the amount of blood glucose was recorded in all experimental groups. Next, all rats were fasted overnight and then the rats were all sacrificed by overdose of ketamine (100 mg/mL) and xylazine (100 mg/mL) in a ratio of 4:1 (v/v) intramuscularly. Blood samples were collected by cardiac puncture for serum biochemical and physiological analysis, the pancreas was taken and preserved in 10% buffered formalin for histopathological examination [30].

***Swertia Chirayata* (Gentianaceae)**

Mechanism of action: Stimulates insulin release from islets.

Albino Wistar mice were fasted for overnight. All group of animals were injected with STZ (Streptozotocin, 100 mg/kg, i. p.) freshly diluted in citrate buffer (10 mmol/L, sodium citrate, pH 4.5) after 10 min. leading induction of NAD (Nicotinamide, 110 mg/kg). The control group received only the vehicle solution CMC (Carboxy Methyl Cellulose) in an equivalent volume. No mortality occurred in the NAD-STZ-treated group during the first day after the diabetes induction. After weaning (day 21), the animals were kept in groups of 6 in collective cages at 23°C and with a full access to food and water for the following 2 weeks and then used for study. Blood samples were collected from retro-orbital plexus. Mice with the fasting blood glucose level of ≥ 200 mg/dl will be considered as diabetic and selected for further pharmacological studies [31]. The test extract was given for 10 days and biochemical investigation was done [32].

***Stevia Rebaudiana* Leaf (**Asteraceae**)**

Mechanism of action: enhancement in insulin production

The traditional use of Stevia extract includes treating diabetes as it is found to increase insulin secretion and sensitivity, according to a clinical study. Isolated mouse pancreatic islet cells have also shown enhancement in insulin production by the action of Rebaudioside A. Stevioside is also known to promote glucose-activated insulin secretion, without affecting fasting insulinemia [33]. Recently, we showed that rebaudioside A potently stimulates the insulin secretion from isolated mouse islets in a dose-, glucose- and Ca^{2+}-dependent manner. Little is known about the mechanisms underlying the insulinotropic action of rebaudioside A. The aim of this study was to define the signalling system by which, rebaudioside A acts. Isolated mouse islets were used in the cAMP[^{125}I] scintillation proximity assay to measure total cAMP level, and in a luminometric method to measure intracellular ATP and ADP concentrations. Conventional and permeabilized whole-cell configuration of the patch-clamp technique was used to verify the effect of rebaudioside A on ATP-sensitive K^+mM glucose, the addition of the maximally effective concentration of rebaudioside A (10-channels from dispersed single β cells from isolated mouse islets. Insulin was measured by radioimmunoassay from insulinoma MIN6 cells. In the presence of 16.7^{-9}M) increased the ATP/ADP ratio significantly, while it did not change the intracellular cAMP level. Rebaudioside A (10^{-9}M) and stevioside (10^{-6}M) reduced the ATP-sensitive potassium channel (K_{ATP}) conductance in a glucose-dependent manner. Moreover, rebaudioside A stimulated the insulin secretion from MIN6 cells in a dose- and glucose-dependent manner. In conclusion, the insulinotropic effect of rebaudioside A is mediated via inhibition of ATP-sensitive K^+-channels and requires the presence of high glucose. The inhibition of ATP-sensitive K^+-channels is probably induced by changes in the ATP/ADP ratio. The results indicate that rebaudioside A may offer a distinct therapeutic advantage over sulphonylureas because of less risk of causing hypoglycaemia.

***Tinospora Crispa* (Menisphermaceae)**

Mechanism of action: Anti hyperglycemic, stimulates insulin release from islets

Twenty four male rats wistar strain were divided into four groups. Each group consisted 6 rats. All rats were adapted for 7 d by giving food and drink to ad libitum. The serum alanine amino transferase (ALT) and aspartate aminotransferase (AST) of rats were measured using colorimetric method (first measurement/day 0). Rats were injected by alloxan monohydrate (Sigma Aldrich USA, CAS: 2244-11-3) at doses of 100 mg/200 bw (g) intraperitoneally. Four days later, the serum ALT and AST of rats were measured (second measurement/day 4) and then were treated by extract appropriate their groups. Group 1 was treated by 2 ml of distilled water orally; group 2,3 and 4 were treated by 70% ethanolic extract of T. crispa L. (EETC) at dose of 100; 200 and 400 mg/200bw (g)/day respectively orally. After 10 d treatment, serum ALT and AST were measured (third measurement/day 14). At the end of this treatment, all rats were killed by cervical dislocation. The liver were taken and stained by HE (Haematoxylin eosin) for histopathologic examination. This study protocol was approved by Health research ethics committee of Faculty of Medicine of Universitas Muhammadiyah Surakarta with no: 228/B.1/KEPK-FKUMS/ IV/ 2016. The blood ALT and AST level were expressed by mean±SD and then analyzed by ANOVA followed LSD test. The analysis of histopathology of liver was done by scoring. Pyknotic nuclei was scored 1, Karyorrhexis (score 2), and karyolysis (score 3). The examination was performed on three fields of view and taken on average each field of view [34].

***Urtifca Dioica* (Urticaceae)**

Mechanism of action: Increase insulin secretion

Forty male Wistar rats, weighting 200-250 g were obtained from the Animal Breeding Center, Jundishapur University of Medical Sciences, and were kept under standard conditions (12/12 light-dark cycle, 20-24oC, 55% humidity) with free access to water and food. All procedures were performed in accordance with the University guidelines for care and use of laboratory animals. One group of rats was assigned as sham group (n=8) and given tap water. Thirty two rats, given daily fresh fructose 10% in drinking water, for eight weeks. Starting from the 6th week, they were randomly divided into four groups (n=8 each) including a control receiving intraperitoneal (IP) vehicle for Urtica dioica, and three other groups receiving single administrations of IP hydro-alcoholic extract of Urtica dioica at 50, 100 or 200 mg/kg. Twenty four hours after the last IP injection, the animals were lightly anesthetized and blood samples were obtained by cardiac puncture. The serum of blood samples were separated and were used to determine levels of blood glucose, insulin, fasting insulin resistance index (FIRI), leptin, triglycerides (TG), total cholesterol, low-density

lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol and hepatic enzymes. Serum glucose levels were determined using glucose-oxidase method. The intra- and inter assay variances were 2% and 4%, respectively. Fifty µl of serum was used for the measurement of insulin by immune radiometric assay (Biosource INS-IRMA Kit). The intra and inter assay variances were 4% and 8%, respectively. Lipid profile, FIRI, alanin transaminase (ALT), and alkaline phosphatase (ALP) were determined by commercial kits and enzymic ways [35].

***Vinca Rosea* Whole Plant (Apocynaceae)**

Mechanism of action: Beta cell rejuvenation, regeneration and stimulation

Five groups of rats, six in each received the following treatment schedule. Group I: Normal control (saline). Group II: Alloxan treated control (150 mg/kg.ip). Group III: Alloxan (150 mg/kg.ip) + Vinca rosea Whole plants extract (300 mg/kg, p.o), Group IV: Alloxan (150 mg/kg.ip) + Vinca rosea Whole plants extract (500mg/kg, p.o), Group V: Alloxan (150 mg/kg.ip) + Standard drug, Glibenclamide (5 mg/kg, p.o). Whole plant extracts and standard drug glibenclamide (5 mg/kg) and saline were administered with the help of feeding cannula. Group I serve as normal control, which received saline for 14 days. Group II to Group V are diabetic control rats. Group III to Group V (which previously received alloxan) are given a fixed dose whole plants extract (300 mg/kg, p.o), (500 mg/kg, p.o) and standard drug glibenclamide (5 mg/kg) for 14 consecutive days. Rats were made diabetic by a single intraperitoneal injection of alloxan monohydrate (150 mg/kg).62 Alloxan was first weighed individually for each animal according to the body weight and then solubilized with 0.2 ml saline (154 mM NaCl) just prior to injection. Two days after alloxan injection, rats with plasma glucose levels of >140 mg/dl were included in the study. Treatment with plant extracts was started 48 h after alloxan injection [36].

***Zingiber Officinale* Rhizome (Zingiberaceae)**

Mechanism of action: Increase insulin level and decrease fasting glucose level

Previously prepared STZ was injected intraperitoneal (1ml/rat) to fasted rats (12 h). After the administration of STZ, the animals were given 5% sucrose solution overnight to prevent hypoglycemia and enhance STZ entrance to β-cells through GLUT2 glucose transporter. After 7 days of STZ injection, hyperglycemic status was estimated using Bayer's Contour meter (Japan) in samples taken from the rat tail vein. Blood glucose levels > 250 mg/dl were considered an indicator for developing Type 2 diabetic and selected for the study. In the present study, 5% glucose solution in drinking bottle was allowed for injected rats to guard against STZ-induced hypoglycemia. Metformin hydrochloride (Shanghai Shi Guibao Medicine Co., Ltd., China) dose for rat was calculated at 500 mg/kg/day and administrated orally to diabetic rats through gastric tube after dissolving in 0.9% (W/V) sodium chloride for 6 weeks. Ethical approval was obtained from the Ethical Committee of King Abdulaziz University (Jeddah, Saudi Arabia) and in accordance with the OECD guidelines for the proper care and use of laboratory animals. Male rats (Rattus rattus) Sprague-Dawley breed were purchased from Animal House, KAU. Thirty male rats, 3 months old, weighing 200–250 g at the age of 8–10 weeks, were kept in standardized rat cages, with light–dark cycle (12/12) at 22°C ± 2°C and left for 1 week for acclimatization. The standard diet and drinking water (provided in graduated polyethylene bottles placed in metal grids in the upper part of the cages) were available ad libitum throughout the study. All doses were given daily for 6 weeks through gastric gavage. Animals were then sorted into six groups (n = 6): G1: control (C) group, which received a vehicle citrate buffer and normal saline. G2: Type 2 nontreated diabetic (D) group provided by standardized food pellets and water ad libitum. G3: Diabetic Type 2 treated with ginger (D + G) group, given previously prepared ginger orally. G4: Diabetic Type 2 treated with metformin (D + M) group, received 500 mg/kg/bw metformin for 6 weeks. G5: normal ginger (G) group, received previously prepared ginger orally [37, 38, 39].

Discussion

Diabetes is a disorder of carbohydrate, fat and protein metabolism caused due to insufficient production of insulin or due to its inhibitory action, which can be considered as a major cause of high economic loss which can in turn impede the development of nations. Before there were drugs from drug companies, natural cures were used and they can still be used today. There are many herbs with strong anti-diabetic properties. Herbal treatments for diabetes have been used in patients with insulin dependent and non-insulin dependent diabetes, diabetic retinopathy, diabetic neuropathy etc. The families of plants with the most potent hypoglycaemic effects include Leguminoseae, Rosaceae, Liliaceae, Bixaceae, Nyctaginaceae, Theaceae, Solanaceae, Lauraceae, Myrtaceae, Malvaceae, Convolvulaceae, Oleaceae, Gentianaceae, Menisphermaceae, Urticaceae, Apocynaceae and Zingiberaceae. The most commonly studied species are: Acacia arabica, Agrimony eupatoria, Aloe barbadensis, Bixa orellana, Boerhaavia diffusa, Camellia sinensis, Capsicum frutescent, Cinnamomum zeylanicum, Eucalyptus globules, Hibiscus rosa, Ipomoea batata, Olea europia, Swertia chirayata, Scoparia dulcis, Tinospora crispa, Urtifca dioica, Vinca rosea and Zingiber officinale. In the experiments, oral glucose tolerance test, streptozotocin and alloxan-induced diabetic mouse or rat were most commonly used model for the screening of antidiabetic drugs. Numerous mechanisms of actions have been proposed for plant extracts. Some hypothesis relates to their effects on Release of insulin from pancrease, Insulin releasing and insulin like activity, Stimulating synthesis and release of insulin. Other mechanisms may also be involved such as Increase insulin concentration and increase insulin binding on insulin receptor, Increase plasma insulin concentration, Increase insulin secretion, Increase insulin secretion and reduction of insulin binding

on the insulin receptor, Increase insulin secretion from clonal pancreatic beta line (BRIN-BD 11), Stimulate insulin secretion from beta cells, Reduce insulin resistance and blood glucose level, Increase insulin release and increase peripheral uptake of glucose, Stimulates insulin release from islets, Insulin-secretagogue activity, stimulates insulin release from islets, Increase insulin secretion, Beta cell rejuvenation, regeneration and stimulation and Increase insulin level and decrease fasting glucose level.

Conclusion

In conclusion, this paper has presented a list of anti-diabetic plants used in the treatment of diabetes mellitus. It showed that these plants have hypoglycaemic effects and can be used to treat various type of secondary complications of diabetes mellitus. Plants have been a good source of medicine for the treatment of various type of disease, still many plants and active compounds obtained from plants have not been well characterized. It is always believed that plant is safe, but so many plant materials are not safe for the human being, that's why toxicity study of these plants should also be elucidated before consumption of these plant materials.

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