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A REVIEW ON ANTIDIABETIC ACTIVITY OF PLANTS BELONGS TO MYRTACEAE FAMILY

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Abstract:

Diabetes is a chronic metabolic disorder characterised by either the insufficient production or the lack of response to a key regulatory hormone of the body's metabolism, insulin. Medicinal plants were used for the treatment of diabetic mellitus in traditional medicine systems of many cultures throughout the world. There are many herbs and plants showing strong anti diabetic activity in myrtaceae family, such as Syzygium cumini, psidium gujava, Campomanesia xanthocarpa, Eucalyptus globulus. This review article is to describe the antidiabetic activity of plants belongs to myrtaceae family.

Keywords:Diabetes, Antidiabetic, Syzygium cumini, Psidium guajava, Eucalyptus globulus, Campomanesia xanthocarpa.

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INTRODUCTION:

MEDICINAL PLANTS POSSESS ANTIDIABETIC ACTIVITY

Diabetes mellitus is the most common endocrine disorder. Medicinal plants were used for the treatment of diabetic mellitus in traditional medicine systems of many cultures throughout the world.The hypoglycemic activity of many medicinal plant products were evaluated and confirmed in animal models as well as in human beings. In some cases, the bioactive principles of the medicinal plants have been isolated and identified. There are several possible mechanisms by which the medicinal plants induced hypoglycemia. These includes enhancing regeneration or revitalization of damaged pancreatic beta cells, and protecting against further damage, enhancing insulin synthesis and secretion from the beta-cells, decreasing glucose absorption from gastro-intestinal system, increasing insulin sensitivity of the tissues, possessing of insulin mimicking effects, and changing the activity of some enzymes involved in glucose metabolism.[1]

ANTIDIABETIC ACTIVITY OF MYRTACEAE FAMILY

Myrtaceae or myrtyle family, of dicotyledonous plants placed within the order myrtales. *Syzygium cumini, Psidium guajava, Eucalyptus globulus, Campomanesia xanthocarpa* belongs here.[2]

SYZYGIUM CUMINI

The *Syzygium cumini* (or Eugenia jambolana) tree belongs to the Myrtaceae family. This is also called as Jamun, Jambul and Jambol in India and Malaya. The barks, leaves and seeds extracts of SC have been reported to possess anti-inflammatory, antibacterial and antidiarraheal effects.The present study was designed to evaluate the anti-diabetic activity of isolated compound mycaminose, Ethyl acetate and Methanol extracts of the SC seeds against STZ-induced diabetic rats.

Fig 1:*Syzygium cumini*

Preparation of plant extract

The SC fruits were first washed well and pulp was removed from the seeds. Seeds were washed several times with distilled water to remove the traces of pulp from the seeds. The seeds were dried at room temperature and coarsely powdered. The powder was extracted with hexane to remove lipids. It was then filtered and the filtrate was discarded. The residue was successively extracted with ethyl acetate and methanol using cold percolation method. The percentage yields were 1.81% in ethyl acetate and 10.36% in methanol.[3]

Preliminary phytochemical screening

The phytochemical screening of SC seed contains alkaloids, amino Acids, flavonoids, glycosides, phytosterols, saponins, steroids, tannins and triterpenoids.

Isolation and identification of the active compound

Five grams of the pure SC seed methanol extract was admixed with 10 g of silica gel (60 - 120 mesh), dried for uniform mixing and the admixture was loaded in a column (5 cm diameter X 50cm height) packed with silica gel (150 g) using hexane as the solvent. The column was eluted with increasing order of polarity gradually from 100% hexane, 100% chloroform and methanol in ethyl acetate (0 - 100%). The fraction eluted at 100% methanol, yield of 350 mg obtained. The compound was obtained as pale brown semi solid. The fraction was characterized by spectroscopy techniques like 1H NMR, 13 C NMR and Mass Spectrum.[4]

Animals

Wistar rats (160 - 180 g) were purchased from King Institute, Chennai for experimental study. They were acclimated to animal house conditions fed with commercial pelleted rats chow, and had free access to water. The experimental protocol was approved by the IAEC (Institutional Animal Ethical Committee) of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animal).

Acute toxicity studies

Acute oral toxicity study was performed as per OECD-423 guidelines (acute toxic class method). Wistar rats (n = 6) of either sex selected by random sampling technique were used for the study. The animals were kept fasting for overnight providing only water, after which the extracts (ethyl acetate and methanol) were administered orally at the dose level of 5 mg/kg body weight by intragastric tube and observed for 14 days. If mortality was observed in 2 - 3 animals, then the dose administered was assigned as toxic dose. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If

mortality was not observed, the procedure was repeated for further higher dose such as 50, 300 and 2000 mg/kg body weight.[5]

Anti-diabetic evaluation

Experimental induction of diabetes: Induction of diabetic mellitus: After fasting for 18 h, 60 rats were injected by intraperitoneally with a single dose of 50 mg/kg streptozotocin after dissolving it in freshly prepared ice-cold citrate buffer (pH 4.5). After the injection, they had free access to feed and water and were given 5% glucose solution to drink overnight to counter the hypoglycemic shock. The development of diabetes was confirmed after 48 h of the streptozotocin injection. The rats having fasting blood glucose level more than 200 mg/dL were selected for experimentation. From, the out of 60 animals, 6 animals were died before grouping and 5 animals were omitted from the study, because mild hyperglycemia (below 150 mg/dL). From the 49 diabetic animals, they were divided into seven groups each having 7 animals.

Collection of blood samples and glucose determination

Blood samples were collected by end tail vein cutting method and blood glucose level was determined by using one touch electronic glucometer.

Experimental protocol

The group I consist of 6 normal control animals. The remaining each group consists of 7 Streptozotocin (STZ) induced diabetic rats. Group I–Normal control animals received 1% SCMC 10 ml/kg per orally for 15 days; Group II–STZ induced diabetic animals received 1% SCMC 10 ml/kg, p.o. for 15 days; Group III and IV– STZ induced diabetic animals received ethyl acetate extract at the dose of 200 and 400 mg/kg p.o. daily for 15 days; Group V and VI– STZ induced diabetic animals received methanolic extract at the dose of 200 and 400 mg/kg daily p.o. for 15 days; Group VII – STZ induced diabetic animals received mycaminose 50 mg/kg daily p.o. for 15 Days; Group VIII–STZ induced diabetic animals received standard drug, glibanclamide 1.25 mg/kg daily p.o. for 15 days. All the group of animals received the treatment by the above schedule for 15 days. Blood samples were collected one hour after drug administration on the day 1, 5, 10 and 15 th day to determine the blood glucose level by electronic glucometer.

Statistical analysis

Data obtained from pharmacological experiments are expressed as mean ± SD. Differences between the control and the treatments in these experiments were tested for significance. p value < 0.05 were considered as significant. From the above experiment we find that the blood sugar levels measured in normal and experimental rats in initial and at the 1, 5, 10 and 15 days of treatment. Streptozotocin-induced diabetic rats showed significant decrease in the levels on blood sugar as compared to normal rats. Oral administration of ethyl acetate and methanol extracts (200 and 400 mg/kg) showed significant decrease ($p<0.05$) in blood sugar level.[6]

PSIDIUM GUAJAVA

Diabetes mellitus is caused by an absolute or relative lack of biologically active insulin, which results in impaired uptake and storage of glucose as well as reduced glucose utilization for energy purposes. Various studies of the common guava, P. guajava, have shown that the bark, fruit and leaves possess anti-diabetic properties. Studies with alloxan or streptozotocin (STZ)-induced diabetic rats and in genetic Leprdb/Leprdb diabetic mice suggest that some of the anti-diabetic effects may be exerted via inhibition of protein tyrosine phosphatase1B (PTP1B) while other studies suggest that the anti-diabetic effects are due to improved glucose metabolism and insulin sensitivity through modulation of insulin-related signalling in muscle or modulation of the activities of carbohydrate metabolising enzymes in liver.[7]

Fig 2: *Psidium Guajava*

MATERIALS AND METHODS

Plant material

Psidium guajava Linn leaves were collected. The leaves were extracted with distilled water for 48 h at room temperature. The extract was filtered, after which it was lyophilized using a VirTis SP Scientific Sentry 2.0 freeze drier. The extract was stored until further use at room temperature.

Animals and diet

Male Sprague-Dawley rats (230–250 g body weight) were procured from the Biomedical Resource Unit (BRU) at Westville Campus of the University of

KwaZulu-Natal. The animals were provided with rat chow diet and normal drinking water ad libitum for the experimental period. The animals were maintained according to the rules and regulations of the University of KwaZulu-Natal.[8]

INDUCTION OF DIABETES

Animals were fasted for 12 h prior to induction. Diabetes was induced in rats by injecting them intraperitoneally with (40 mg/kg.body weight) streptozotocin dissolved in 0.1 M citrate buffer, pH 4.5. After one week diabetic rats with fasting blood glucose concentration of 12–14 mmol/l were used for the study. Control animals were injected with citrate buffer only. Animals were divided into four groups of 6 rats each. NC and DC groups consisted, respectively, of normal and diabetic control rats given vehicle (distilled water) orally. The treatment groups NPG and DPG consisted, respectively, of normal and diabetic rats, that were supplemented daily with PG via oral gavage at a dose of 400 mg/kg body weight. The animals were treated for 14 days after which they were euthanized with an overdose of isofluorane in the anaesthetic chamber followed by an immediate cardiac puncture. Blood samples were collected into tubes containing heparin and were centrifuged at 3000 g for 10 min to obtain plasma which was stored at -20 ◦C for further analysis. A portion of the pancreas was removed and fixed in 10% formalin. Skeletal muscle was dissected from the hindquarter, snap frozen in liquid nitrogen before being stored at -20 ◦C until analysed.[9]

Glucose tolerance test

To measure the glucose tolerance ability of treated and untreated animals, the oral glucose tolerance test (OGTT) was performed after two weeks of treatment using a laboratory protocol. Animals were fasted for 12 h prior to the OGTT. To perform this test, a single dose of glucose solution (1 g/kg b.w.) was given orally to each animal. The levels of glucose in blood drawn from the lateral tail vein were measured at 0, 15, 30, 60, 90 and 120 min after the ingestion of glucose. Estimation of glycogen phosphorylase and glycogen synthase activity in muscle.The glycogen synthase activity was assayed radio-chemically. The activity of glycogen synthase is expressed as nmoles UDPG converted to glycogen/min/mg protein. Glycogen phosphorylase was assayed radio-chemically in the reverse direction, by measuring the incorporation of radiolabel into glycogen in presence of 1 μCi/ml D-[U-14C] glucose-1-phosphate and 22.3 mM glucose-1-phosphate. Its activity is expressed as nmoles D-glucose-1-phosphate converted to glycogen/min/mg protein.[10]

Western blotting

Protein expression levels of glycogen phosphorylase and glycogen synthase were determined by Western blotting. The muscle samples were homogenized, after which homogenates were centrifuged (12,000 g, 20 mins at 4 ◦C). The supernatant obtained was kept at -80ºC and used for further analysis. The protein concentration was determined by the Biuret method. Subsequently, SDS PAGE and immunoblotting were conducted, the primary antibody (anti-GP or anti-GS) was overlaid on nitrocellulose membrane with shaking at room temperature for an hour. The membrane was washed and probed with a secondary antibody. The protein samples were visualized using a Syngene G-BOX Chem XR5, Vacutec following a reaction of NBT/BCIP substrate with the IgG alkaline. Estimation of glycogen content

Gas chromatography-mass spectrometric (GC–MS) analysis

The aqueous extract of the leaf of Psidium guajava was subjected to GC–MS analysis using a laboratory protocol. The column used was a HP-5MS capillary column with an internal diameter of 30 cm × 0.25 mm and a film thickness of 0.25 μm. The carrier gas was ultra-pure helium with a flow rate of 1.0 mL/min and a linear velocity of 37 cm/sec., the injector temperature being set at 250 ◦C. Oven temperature was initially set at 6◦C and programmed to increase to 280 ◦C at the rate of 10 ◦C/min with a hold time of 4 min at each increment. Sample injections of 2 μL were made in the splitless mode with a split ratio of 20:1. The compounds were identified by direct comparison of the retention times and mass spectral data and fragmentation pattern with those in the National Institute of Standards and Technology (NIST).[11]

STATISTICS

All data were expressed as means ± standard error of means (SEM). Statistical comparison between groups was done using one-way analysis of variance (ANOVA). Values of $P < 0.05$ were considered statistically significant.

From our findings, Psidium guajava leaf aqueous extract was shown to have hypoglycaemic effect in STZ induced diabetic rats and restored synthase activity depressed by diabetes which was accompanied by reduced glycogen phosphorylase activity and increased glycogen levels. The antidiabetic effects of PG may be associated with the presence of phenolic compounds and triterpenoids whose activity may have also led to amelioration of damage to the pancreas caused by STZ.[12]

EUCALYPTUS GLOBULUS

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia. It may be due to a decrease in the synthesis of insulin (Type-I diabetes) or due to a decrease in the secretion of insulin from beta-cells of islets of the pancreas (Type-II diabetes). Eucalyptus globulus Labill (Myrtaceae) is a fast-growing, evergreen tree, native to Tasmania and south-eastern Australia. Leaves from Eucalyptus globulus are reported to contain a high content of eucalyptol (cineol) together with rutin, terpineol, sesquiterpene, alcohols, aliphatic aldehydes, isoamyl alcohol, ethanol, terpenes, and tannins. A study in streptozotocin (STZ)-diabetic mice confirmed the antihyperglycaemic effectiveness of *Eucalyptus globulus*.[13]

Fig 3: *Eucalyptus globulus*

MATERIAL AND METHODS

Plant material

Eucalyptus globulus Labill leaves were collected fresh from a garden in Zahedan University of Medical Sciences (ZUMS). The plant was identified and verified at the Herbarium of Botany Directorate in Sistan and Baluchestan University, Zahedan, Iran. A voucher specimen was deposited in the Botany Department of Sistan and Baluchestan University.

Preparation of eucalyptus-incorporated diet and aqueous extract of Eucalyptus globulus:

The leaves were homogenized to a fine powder and stored at room temperature (20 ± 2°C) until use. For the animals, eucalyptus was incorporated into a powdered diet, thoroughly mixed, distilled water was added, and it was mixed into a stiff paste.The mixture was then pelleted and dried at 45°C.The control diet was prepared by the same method to ensure there were no end differences in vitamin and mineral content due to the drying process. Aqueous extract of eucalyptus (AEE) was prepared by 15 minutes decoction of the powdered material, as described by Gray and Flatt.[14]

Animals

The study was performed on 50 matured normoglycaemic male albino rats (Rattus norvegicus) of Wistar strain. weighing 200–250 g, separately housed in cages(one rat per cage), with free access to water and food. The animals were maintained in a room at 23 ± 2°C with a fixed 12-hour artificial light period, and the air was adequately recycled. All animals were fed with standard rodent diet with the following composition (w/w): 20% protein, 3% fat, 2% fibre,6% minerals, and 69% starch and vitamin supplements. All animals received humane care as outlined in the guide for the care and use of laboratory animals.[15]

Experimental design

Fifty rats were divided into the five following groups (n = 10):

(I) Control group (C): rats of this group received rodent diet and tap water. After one week they received intraperitoneal vehicle (0.15 M NaCl with 100 mM sodium citrate buffer).

(II) Diabetic group (D): in this group diabetes was induced by a single intraperitoneal injection of streptozotocin (60 mg/kg of body weight in 0.15 M NaCl with 100 mM sodium citrate buffer, pH 4.5).

(III) Treated control group (TC): healthy rats received eucalyptus supplemented diet and drinking water. 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): these groups received, respectively, 20 and 62.5 g/kg eucalyptus in the diet, and 2.5 g/L AEE in drinking water, from one week after induction of diabetes by streptozotocin.

The eucalyptus treatment began one week after induction of diabetes and lasted for four weeks, and then the rats were killed. Food and fluid intake of all groups were measured daily. Body weight and blood glucose were measured every week.[16]

Glucose measurement

Blood samples were collected from the tail vein. Blood glucose levels were measured by standard method of oxidase-peroxidase paired enzyme.

Preparation of tissues

At the end of the experiment, and after overnight fasting, all animals were sacrificed. The pancreases were quickly removed, placed in cold saline solution and trimmed of adipose tissue, and weighed, and volumes were measured using immersion method and fixed in modified Lillie's solution for one week at

room temperature. Using the orientator method, 10–12 isotropic uniform random sections were obtained. Briefly, each pancreas was placed on a circle that was divided into 36 equal sectors, and was sectioned along the line bearing a randomly selected number. The sectioned surface of the bar was placed on the 0–0 direction of the circle with 97 unequal sinus-weighted divisions and the second cut was done. After routine histological processing, the new surface was embedded in paraffin, sectioned (5 µm thickness) and stained by modified aldehyde fuchsin histochemical method.

Statistical analysis:Data are presented as the means ± SE for each investigated parameter. One-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons were used to compare differences between the experimental groups. The level of significance was set at $p < 0.05$.

The present study showed that the treatment of diabetic rats with Eucalyptus globulus for four weeks compensated the diabetic state and significantly reduced blood glucose levels in comparison to the diabetic rats.Streptozotocin injection results in diabetes mellitus, which may be due to selective destruction of beta cells . STZ-induced diabetes is characterized by weight loss, increase of water and food intake, and high blood glucose levels . In treated diabetic rats (TD1,2), body weight significantly increased, and water and food intake significantly decreased, compared to the D group.[17]

CAMPOMANESIA XANTHOCARPA

Campomanesia xanthocarpa Berg, popularly known as gabiroba, is a common species in the forests of the Southern, Southeastern and Midwestern regions of Brazil, and is also found in Uruguay, Paraguay and Argentina. The infusion prepared from its leaves is commonly used as a depurative, anti-diarrheic, cleanser, anti-rheumatic, and to lower blood cholesterol . Recently, confirmed that it is popularly used to reduce obesity. Despite its popular use, there is scant pharmacological information available on this plant. The chronic treatment of obese rats with the infusion of the leaves of C. xanthocarpa led to a significant decrease in body mass, as well as a reduction in glycemia. Since C. xanthocarpa caused a hypoglycemic effect in obese rats, the objectives of this research were to verify the effects of the chronic treatment of normal and streptozotocin-induced diabetic rats using a leaf decoction of C. xanthocarpa (20 g/L) on physiological, biochemical and histopathological parameters.[18]

Fig 4: *Campomanesia xanthocarpa*

MATERIAL AND METHODS

Plant material

Campomanesia xanthocarpa leaves were collected.The leaves were kept in a dry and ventilated place, protected from light, and were dried and powdered. The decoct (20 g/L) was prepared daily, boiled for 10 minutes and when reaching room temperature, the solution was filtered and administered to the rats as a drinkable solution.[19]

Rats and experimental design

Male Wistar rats weighing. The rats were housed in an environmentallycontrolled room with a 12 h light &12 h dark cycle at a constant temperature of 23 °C. A freshly-prepared solution of streptozotocin (STZ, 70 mg/kg/bw) in 0.1 M citrate buffer, pH 4.5 was injected intraperitoneally to rats that had fasted overnight. One week later, blood samples were collected from the orbital sinus, and rats with fasting blood glucose (FBG) levels above 200 mg/dL (11.1 mmol/L) were selected for the experimental protocol. During a 21-day period of treatment, normal and STZ-treated rats were fed with 40 g/day of pelleted food and divided into four drinking groups:

- Group I (WC): water (negative) control; control ratswhich received 100 mL of water a day (n=15).
- Group II (WD): water (untreated) diabetic; STZ treated rats which received 100 mL of water a day (n=16).
- Group III (DC): decoct (positive) control; control rats which received 100 mL of C. xanthocarpa (20 g/L) decoction a day (n=19).
- Group IV (DD): decoct diabetic; STZ-treated rats which received 100 mL of C. xanthocarpa (20 g/L) decoction a day (n=19).

At the end of the second week of treatment, the rats were transferred to individual metabolic cages where they were kept for a further week. During this period, the total amount of food and drink ingested were measured daily, as was urine volume. Throughout the experimental period, blood samples were collected weekly from the eyes under mild ether anesthesia and collected. After centrifugation, the plasma samples

were stored frozen for later biochemical analysis. On the last day of the treatment, after a 12-hour period of fasting, the rats were sacrificed by decapitation after mild ether anesthesia. Blood and organ samples (liver, diaphragm, kidney and pancreas) were collected. The blood samples were obtained by means of heart puncture with 0.1mL of sodium citrate. After centrifugation, the plasma was separated and stored frozen for the subsequent biochemical assays. The body weight of the rats was also monitored.[20]

Biochemical analysis

Blood glucose was determined by the glucose oxidase method using glucose diagnostic kits HK-Liquiform. Plasma triglycerides and total cholesterol were also determined using diagnostic kits: Triglycerides GPO-ANA and cholesterol-liquiform. Liver samples used for glycogen determination were collected using the freeze-clamp procedure with aluminum tongs and stored frozen.

Histological analysis

For the histopathological analysis, samples of the liver, pancreas and kidney were preserved in 10% formaldehyde for 24 hours and processed following the routine procedure. Pancreas samples were also stained with Gomori's aldehydefuchsin, a procedure for identifying the effects of the treatments on β cells. At the end of the treatment, the diabetic rats that received C. xanthocarpa decoction showed a 26% reduction in blood glucose ($p < 0.05$) in relation to the untreated diabetic group.[21]

DISCUSSION:

The present study showed that the treatment of diabetic rats with syzygium cumini, psidium guajava, Eucalyptus globulus and campomanesia xanthocarpa compensated the diabetic state and significantly reduced blood glucose levels. Streptozotocin injection results in diabetes mellitus, which may be due to selective destruction of beta cells. STZ-induced diabetes is characterized by weight loss, increase of water and food intake, and high blood glucose levels. In treated diabetic rats body weight significantly increased, and water and food intake significantly decreased.

CONCLUSION:

Diabetes is a disorder of carbohydrate, fat and protein metabolism caused due to insufficient production of insulin or due to its inhibitory action. There are many herbs and plants showing strong anti diabetic activity in myrtaceae family, such as Syzygium cumini, psidium gujava, Campomanesia xanthocarpa.

In this review, phytochemicals such as terpenoids, phenolics,alkaloids,flavounoids shows anti diabetic activity.In this study anti diabetic activity of myrtaceae family plants were screened by using oral glucose tolerance test, streptozotocin and alloxan induced model.

As we can conclude that, syzygium cumini shows a decrease in blood sugar level of streptozotocin induced diabetic rats. Also Psidium guajava leaf aqueous extract, Eucalyptus globulus and Campomanesia xanthocarpa was shown to have hypoglycaemic effect in streptozotocin induced diabetic rats. It showed that these plants have hypoglycemic effects and can be used to treat various type of secondary complications of diabetes mellitus. And the review showes that these studies are useful to discover a new natural antidiabetic drug which could be a great promise.

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