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ANTI DIABETIC POTENTIAL OF HERBAL PLANTS AND POLYHERBAL FORMULATION SOURCE LIKE PHYLLANTUS EMBLIKA AND ALOE BARBADENSIS

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ABSTRACT:

Diabetes mellitus is caused by decreased insulin secretion. The people throughout the world increasingly affected by diabetes mellitus, a global problem. Due to side effects and other reasons usage of oral hypoglycemic agents is reduced. Globally, there will be an increase in the usage of herbal medicines for treating various diseases was reported. According to WHO all herbal medicines should be scientifically evaluated for their activities.

In India from ancient time onwards herbal medicines were used to cure many diseases. Diabetes mellitus is cured by many medicinal plants. Many formulations were also formulated to treat diabetes mellitus but there is a lack of scientific validation so, the aim of this study is to select and scientifically validate a traditional polyherbal formulation. This review work is a small step towards scientifically studying the traditional polyherbal antidiabetic formulation, so as to standardize and improve the formulation for the benefit of humankind**.** traditional polyherbal formulation. This review work is a small step towards scientifically studying the traditional polyherbal antidiabetic formulation, so as to standardize and improve the formulation for the benefit of humankind**.**

This dreadful disease is found in all parts of the world and is becoming a serious threat to mankind health. It is caused by the deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. There are lots of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported up to this date.

KEYWORDS:

Antihyperglycemic, antioxidant, metformin, streptozotocin, Diabetes mellitus

INTRODUCTION:

According to WHO, diabetes mellitus will be the single largest non-communicable disease worldwide by the year 2025 with the largest diabetic population in India. Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipedemia, hyperaminoacidemia, and hypoinsulinaemia it leads to decrease in insulin, secretion and insulin action. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides, α-glucosidase inhibitors and glinides. Herbal product have played important role in health care and prevention of many diseases including diabetes.

There are 2 major types of diabetes:

type 1 or insulin dependent, type 2 or non–insulin dependent, and gestational diabetes. The total number of patients with diabetes worldwide is expected to double in 2005-2030. It has been found that diabetes mellitus is a major cause of morbidity and mortality with an increasing prevalence due to sedentary lifestyle and obesity, indicating
that research on the prevention and treatment of diabetes deems
critical.Type 2 diabetes mellitus is the most common form of diabetes accounting for 90% to 95% of patients. The prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and 4.4% in 2030. According to the World Health Organization, diabetes will be the seventh leading cause of death in 2030.

A) Aloe vera and Aloe barbadensis

Figure 1: Herbal Plant Aloe Vera Used For Antidiabetic

Aloe (Asphodelaceae), a popular houseplant, has a long history as a multipurpose folk remedy. The plant can be separated into two basic products: gel and latex. Aloe vera gel is the leafpulp or mucilage, aloe latex, commonly referred to as “aloe juice,” is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats. Treatment of chronic but not single dose of exudates of Aloe barbadensis leaves showed hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also showed hypoglycemic effect in diabetic rats. This action of Aloe vera and its bitter principle

is through stimulation of synthesis and/or release of insulin from pancreatic beta cells. This plant also has an anti-inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice. Aloe vera (L.) Burm. fil. (synonym A. barbadensis Miller) (Tamil – Southakathalai, Hindi – Ghikanvar), is a cactus-like plant with green, dagger-shaped leaves that are fleshy, tapering, spiny, marginated and filled with a clear viscous gel. It is also known as 'lily of the desert', the 'plant of immortality', and the 'medicine plant' with qualities to serve as alternate medicine.

B) Phyllanthus emblica(Amla)

Sultana Z et al investigated antidiabetic effect of ethanolic extract of *Phyllanthus emblica* Linn. fruits in experimental animal models. Study showed significant inhibition of intestinal disaccharidase activity results in reduction of sucrose absorption. Arijit C et al studied about the evaluation of antidiabetic activity of polyherbal formulation in streptozotocin- induced diabetic rats. The varied concentration of formulation significantly lowers the blood glucose level, total cholesterol, triglycerides and low density lipoprotein. Krishnaveni M et al studied about the antidiabetic and antihyperlipidemic properties of *Phyllanthus emblica* Linn. (Euphorbiaceae) on streptozotocin induced diabetic rats. This study shows about the antidiabetic and its beneficial effects on lipid profile. Arunvanan M et al reviewed about the overview on anti diabetic activity of siddha medicinal plants which reveals its antidiabetic activity through pancreatic and extra pancreatic mechanism.

Anti-diabetic activity studies of herbomineral formulation for treatment of diabetes were evaluated. This study evaluate the antidiabetic activity of the formulation containing five different herbs and two minerals in streptozotocin (STZ 50 mg/Kg ip single dose) induced diabetic rats. The two formulations F1 (500 mg/Kg) and F2 (1000mg/Kg) had showed significant reduction in blood glucose level. The development of an antidiabetic formulation and its inhibitory activity against α -amylase and α– glucosidase were performed. The results showed that the formulation had a significant inhibitory activity on α-amylase and α- glucosidase and was less than that of acarbose. The plants that are formulated possess potent antidiabetic activity.

The nano-encapsulated form of *Phyllanthus emblica e*xtract increases its therapeutic effects as antidiabetic and antioxidant in rats. The results showed significantly decreased blood glucose alterations in the expression of glycolytic and gluconeogenic genes, DNA damage and increased the activity of glutathione peroxidase enzyme.

The anti-diabetic activity of commercially available extracts of *phyllanthus emblica* in streptozocin induced diabetic rats was performed. The results showed that commercially available *Phyllanthus emblica* extracts have significant hypo glycemic activity. Mali PR.
Performed a study of antidiabetic activity of *Phyllanthus emblica* linn and *Curcuma longa* Linn on alloxan induced mice. The extracts were effective in regulating the bio chemical indices associated with diabeties mellitus such as glycogen content and the activities of glucokinase and glucose-6- phosphate.

evaluated a systematic review of the antioxidant, antidiabetic and anti-obesity effects and safety of triphala herbal formulation. This study showed activities like anti-diabetic, antioxidant and lowers cholesterol. An investigation of antidiabetic effect of ethanolic extract of

Phyllanthus emblica Linn fruits in experimental animal models were studied and results showed that ethanolic extract has significant antidiabetic effects.

Mechanism of Action of Herbal Antidiabetics:

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as-

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2^{nd} messenger) stimulation
- Inhibition in renal glucose reabsorption
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes
- Reduction in insulin resistance
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells
- Regenerating and/or repairing pancreatic beta cells
- Increasing the size and number of cells in the islets of Langerhans
  Stimulation of insulin secretion
- Stimulation of glycogenesis and hepatic glycolysis
- Protective effect on the destruction of the beta cells
- Improvement in digestion along with reduction in blood sugar and urea
- Prevention of pathological conversion of starch to glucose
- Inhibition of β -galactocidase and α–glucocidase
- Cortisol lowering activities
- Inhibition of alpha-amylase

Plant material :

The fresh leaves, stems, and flowers of aloe vera and phyllantus emblica were collected from areas surrounding M (Karnataka, India).

No specific permission obtained for the collection of the plant matenal st plant is available in plenty around Mysore, and it an endangered or protected species. The leaves, stems, and flowers were dried under shade and powdered by the help of mechanical process.

Animal care and ethical approval:

In the present study. 10-week-old male Wistar albino rats, weighing about 150-170 g bzw. were used in the present study. Animals were obtained from the Central Animal Facility, University of Mysore. Mysore, and acclimatized to the laboratory conditions for 2 weeks. All animals received regular human care. They were randomly distributed into different groups consisting of six per cage and fed standard laboratory diet provided by the Central Animal Facility. University of Mysore, Mysore. Clean drinking water (ad libitum) was supplied throughout the study period. The room temperature was maintained at 22°C 3°C and the relative humidity at 30%-70%, with 12-h light and dark cycle. Experiments were complied with the rulings of the "Committee for the Purpose of Control and Supervision of Experiments on Animals" (CPCSEA) Mysore, India (122/GO/ReBi/1999/CPCSEA dated June 3, 2015). The study was permitted by the Institutional Ethical Committee of Mysore, India (UOM/IAEC/15/2016). The investigation was carried under the supervision of expertise in animal handling and care.

Oral glucose tolerance test:

in nondiabetic rats The oral glucose tolerance test was executed in nondiabetic rats according to the method described by Barik et al. The rats were fasted overnight (16 h) before the test. Fasting blood glucose level in each rat was tested before the test. Overnight-fasted rats (n=24) were divided into four groups. Control (Group 1) was provided with an equal volume of distilled water. Group 2 and 3 rats were administered with active fraction at doses of 25 and 50 mg/kg b.w. through oral gavage. Group 4 rats were fed with glibenclamide at a dose of 25 mg/kg b.w. Glucose (2 g/kg b.w.) was fed 30 min after the administration of extracts. Blood was drawn i from the retro-orbital plexus at 30, 60, 90, and 120 min of extract administration, and plasma glucose level was determined by a blood glucose meter. All the data were expressed as the average level in six experimental animals in one group.

Induction of diabetes:

Noninsulin-dependent diabetes mellitus (Type-2) was induced by intraperitoneal injection of NA at 230 mg/kg bw.insaline. After 15 min, a freshly prepared STZ at a concentration of 65 mg/kg bw. dissolved in 0.1 M citrated buffer (pH 4.5) was intraperitoneally injected. After 8 h of SIZ-NA administration, the rats were kept on 15% glucose solution bottles for the next 24 h in their cages to prevent hypoglycemia After 48 h of STZ-NA administration, the diabetic state was assessed by measuring the fasting blood glucose level using a glucometer (Glucocard Vital Strip Method). The rats with serum glucose above 230 mg/dL, as well as with polydipsia, polyuria, and polyphagia, were selected and equally distributed into different groups, except to G1 and G6.

Experimental design:

A total of 36 rats were divided into six groups as follows:

Group 1: Normal untreated rats

Group II: Diabetic untreated rats Group II: Diabetic rats treated with 25 mg active fraction/kg b.w./day for 28 days.

Group IV: Diabetic rats treated with 50 mg active fraction/kg how./day for 28 days Group V: Diabetic rats treated with 25 mg glibenclamide/kg b.w./day for 28 days)

Group VI: Normal rats treated with 50 mg active fraction/kg b.w./day for 28 days.
Active fraction of I. frutescens was dissolved freshly in 0.5% carboxy methyl cellulose to get the desired concentration as per the dose level and administered to animals daily through oral route by gavage for a period of 28 days. During the study, daily feed intake and weekly b.w. variations were monitored for all the experimental rats.

Analysis of hematological parameters:

During the experimental trial, blood samples were collected humanely from rats treated with mild ether anesthesia by retro-orbital plexus puncture method using a fine capillary tube. Blood was collected in tubes containing dipotassium ethylene di-amide tetra acetic acid anticoagulant and without anticoagulant for clinical chemistry. The blood samples collected in the tubes without anticoagulant were centrifuged at 3000 rpm for 10 min to obtain serum. Fasting blood glucose levels were checked using the glucometer (Glucocard Vital Strip Method) from all the animals on day 1 (48 h after the STZ administration and before the test sample administration), 7, 14, 21, and 28 days of the study period. . Blood plasma was recovered for the determination of plasma insulin levels. Glycosylated hemoglobin was estimated according to the method described by Sudhakar and Pattabiraman.

Histopathological studies:

Excised pancreas and liver samples were washed in ice-cold
normal saline, patted dry, and immediately preserved in 10% Neutral buffered formalin (NBF). They were processed in an automatic tissue processor and embedded In paraffin wax Sections of 5 jum were cut and stained with hematoxylin and eosin, and later, the microscopic slide were photographed using a light microscope.

Statistical analysis :

The raw data obtained from the present study were subjected to one-way analysis of variance with Duncan multiple range test for the data on b.w., and clinical chemistry parameters were analyzed using Graph Pad. Prism Software, Increase (version 5.01). All analyses and comparisons were evaluated at the 95% level of confidence ($P<0.05$). The data generated were compared with the control group animals.

Results:

Oral tolerance:

The oral glucose tolerance test was carried out to study the effect of active fraction on glucose metabolism. Administration of distilled water and glibenclamide was considered as negative and positive control, respectively. Animals treated with 25 and 50 mg/kg b.w. of extracts and glibenclamide (25 mg/kg b.w.) showed a decrease in blood glucose level (149.33 mg/dl, 1365 mg/dl, and 128.5mg/dl, respectively) when compared with the control group (15133 mg/dl) in 30 min after the administration of glucose. After 1 h. a noticeable decrease was observed in groups treated with active fraction and glibenclamid which shows that they have played a significant role in synthesis of glycogen from glucose. After 120 min blood glucose level of rats treated with active fraction a 50 mg/kg b.w was approximately similar to the counter group (81.5mg/dl.) without causing a hypoglycemic state.

Hypoglycemic activity in normal and streptozotocin-induced diabetic rats:

According to the results obtained, 239-fold increase ($P<0.05$) in the fasting blood glucose levels was observed in SIZNA-induced diabetic untreated rats when compared to diabetic rats treated with active fraction at 50 mg/kgbw [Table 11. Oral administration of the purified fraction 25 and 50 mg/kg bw, to the diabetic rats gradually lowered the blood glucose level after the 7h day of administration, reaching a level of 192.5 and 166.0 mg/dL, respectively after 28 day. The results indicate 40.18% and 55.98% fall in blood glucose levels of diabetic rats on administration of 25 and 50 mg/kg b.w. of purified fraction, respectively Glibenclamide-treated diabetic rats showed 63.03% fall in blood glucose levels at 25 mg/kg b.w.

Table 1: Summary of fasting blood glucose (mg/dL) values

Group	Treatment (mg/kg)	Day 0	Day 7	Day 14	Day 21	Day 28
G1	Normal control rats	86.58±08.4^{a}	89.33±11.64^{a}	87.83±08.06^{a}	87.33±04.80^{a}	83.67±06.83^{a}
G2	diabetic untreated rats	307.33±19.37^{b}	316.50±17.71^{c}	326.67±18.37^{d}	341.33±12.32^{d}	352.33±11.91^{a}
G3	Diabetic + active fraction (25 mg/kg)	321.83±16.25^{c}	302.83±16.22^{b}	273.50±15.82^{b}	223.67±20.68^{c}	192.5±20.8^{d}
G4	STZ - 40 Active fraction - 50 mg/kg	358.00±21.00^{d}	332.17±21.79^{d}	302.17±20.91^{c}	230.67±18.58^{c}	166.0±0.5.92^{c}
G5	Diabetic + glibenclamide (25 mg/kg)	331.00±17.40^{c}	314.00±16.20^{c}	261.67±12.36^{b}	175.83±14.18^{b}	134.83±18.0^{b}
G6	Normal rats + active fraction (50 mg/kg)	87.33±6.16^{a}	90.33±9.24^{a}	85.17±5.95^{a}	89.00±5.06^{a}	86.33±5.75^{a}

Values are mean±SD (n=6); Mean values within the same column with different lowercase superscripts are significantly different (P<0.05) according to Duncan multiple range test. Day 1 refers to 48 h after the STZ administration. SD=Standard deviation, STZ=Streptozotocin

Effect of purified fraction on body weight of normal and diabetic rats:

Diabetic untreated rats showed significant (P<0.05) reduction in b.w. when compared to normal control rats. In glibenclamide-fed positive control rats, b.w.increased from 157.5 g to 167.08 g in 28 days of the experimental period. Similarly, on administration of active fractions, a gradual increase in b.w. was observed in diabetic-induced rats. Normal rats fed with active fraction showed b.w. almost similar to control rats.

Effect on plasma insulin glycosylated heamoglobin, and hepatic glycogen levels

The plasma insulin level of the control and experimental groups of rats .there was a significant variation in the plasma insulin levels of diabetic control group as compared to normal rats.

Table 2: Summary of weekly animals body weight (g)

Group	Treatment and dose	Treatment period (days)		
		Day 1	Day 15	Day 28
G1	Control	156.83±5.75^{a}	180.08±4.08^{a}	190.08±21.10^{c}
G2	Diabetic untreated rats	163.00±6.14^{b}	153.83±6.18^{a}	146.17±5.91^{a}
G3	Diabetic + active fraction (25 mg/kg)	164.67±4.31^{b}	172.17±13.78^{a}	178.25±4.38^{b}
G4	Diabetic + active fraction (50 mg/kg)	158.50±5.68^{a}	166.67±8.33^{b}	172.00±13.00^{b}
G5	Diabetic + glibenclamide (25 mg/kg)	157.50±6.47^{a}	163.83±5.34^{b}	167.08±8.02^{b}
G6	Normal rats + active fraction (50 mg/kg)	163.42±4.60^{b}	187.33±7.99^{a}	192.00±22.04^{c}

Values are mean±SD (n=6); mean values within the same column with different lowercase superscripts are significantly different (P<0.05) according to Duncan multiple range test. SD=Standard deviation

Effect on serum lipid profile:

Analysis of serum lipid profile in control rats showed the normal range of HDL, LDL, TG, and TC On induction of diabetes, TC significantly (P < 0.05) increased from 1025 to 138.0 mg/dl. Similarly, LDL. VLDL, and TG levels were also found to elevate on induction of diabetes, while HDL level decreased from 49.67 to 39.83 mg/ dl. Treatment of diabetic rats with active fraction and glibenclamide resulted in the significant increase inter HDL-cholesterol (HDL-c) level and decrease in elevated TC, TG, and LDL cholesterol (LDL-c) level, when compared to diabetic rats, which is explained by the increase in plasma insulin level after treatment.

Effect on serum glutamic oxaloacetic transamines and serum glutamic pyruvic transaminase :

As per the results obtained, a significant increase in serum SGOT and SGPT levels was observed in STZ-induced diabetic control rats [Table 3). In glibenclamide-fed positive control rats, SCOT and SGPT levels increased in diabetic rats. Similarly, administration of active fraction at 50 mg/kg b.w. to the diabetic rats for 28 days maintained SGOT and SGPT level in the normal range.

Histopathological studies :

in the normal control rats, the islates of langerhance in pancreas depicted normal acini and normal cellular population .however in diabetic control rats minute and reduced number of islet cells was observed.

DISCUSSION:

The incidence of diabetes has continued to prevail despite large number of discoveries and invention of newer drugs to treat or prevent the condition. The persistent hyperglycemia causes long-term dysfunction and damage of various organs, especially the tissues requiring insulin for glucose uptake. Management of diabetes is therefore a major challenging task be of adverse effects associated with synthetic dog Over the years, many plants are being generally used to treat diabetes mellitus Plants are known to exhibit hypoglycemie, hypolipidemic, and antioxidant activity due to the presence of flavonoids, ellagic acids, phenolic acids, phytosterols, gallotannins, and other relate polyphenols. Earlier literature reveals the aloe vera and phyllantus emblica leaves in the treatment of diabetes . However, scientific validation for the therapeutic efficacy is limited. In this context, the pre investigation was carried out to study the anti-diabetic effect of aloe vera and phyllantus emblica in diabetic-induced albino wister rats.

Oral glucose tolerance test was carried out initially to provide the evidence that active fraction obtained from aloe vera and phyllantus emblica has the ability to lower blood glucose especially in normal glycemic rats. Accordingly, the results clearly indicate that after 120 min, blood glucose level of rats treated with active fraction was similar to the control group without causing any hypoglycemic state. polyphenol

Extract of aloe vera and phyllantus emblica has shown to reduce blood glucose within 1h at a concentration of 200 mg/kg.

CONCLUSION:

The results of study that showed that active fraction obtained from methanolic extract of aloe vera and phyllantus emblica possessed antidiabetic properties as shown in its ability, to reduce blood glucose level of STZ-indused diabetic rats. This confirmation justifies its use in ethanomedical medicine for the treatment of diabetes .further studies should be undertaken to identify the active antihyperglycemic compound comprehensive chemical pharmacological investigation should be carried out to isolet the active compound and appropriate elucidation of its mechanism of action .the result suggests that it is worth undertaking further studies on possible usefulness of the aloe vera and phyllantus emblica in diabetes mellitus.

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