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ANTIDIABETIC ACTIVITY OF POLYHERBAL FORMULATION CONTAINING CITRULLUS COLOCYNTHIS, PIPER NIGRUM, ASPARAGUS RACEMOSUS, CINNAMOMUM TAMALA (CPAC) IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

The aim of the present study was to evaluate the antidiabetic activity of polyherbal formulation containing Citrullus colocynthis, piper nigrum, Asparagus racemomusin, and Cinnamomum tamala alloxan induced diabetic rats. The polyherbal CPAC, is one of such herbal remedies prepared from the fruit of Citrullus colocynthis, seeds of piper nigrum, roots of Asparagus Racemomus and leaves of Cinnamomum Tamala used to evaluate antidiabetic activity. The dose of the formulation was determined from acute toxicity study. The polyherbal formulation of CPAC had shown significant protection and lowered the blood glucose levels to normal in glucose tolerance test. The antidiabetic effect of polyherbal formulation was studied in Alloxan (120mg/kg b.w., i.p.) induced diabetes in male wistar rats for doses 200 mg/kg b.w. and 400 mg/kg b.w. (p.o.) daily for 21 days, and the effect was compared with oral dose of 5mg/kg, b.w. glibenclamide. The administration of extracts were continued for 21 days was evaluated through the estimation of HDL, LDL, VLDL levels, SGPT and SGOT levels, Total cholesterol levels and Total triglycerides levels. Blood samples were collected through the tail vein on days 1, 7, 14 and 21 after drug administration and the blood glucose levels were estimated using Accu-check glucometer. Diabetes caused by Alloxan treatment increases the level of glucose and biochemical parameter in blood sample but treatment with polyherbal formulation, protects from diabetes and significant decrease the elevated glucose, LDL, VLDL levels, SGPT and SGOT levels, Total cholesterol levels and Total triglycerides levels, increased in HDL level.

KEYWORDS: Polyherbal Formulation, Alloxan, Glibenclamide, Tween 80 (5%), Ethanol, Hexane, 5% Glucose.

INTRODUCTION

Diabetes mellitus is a common endocrine disease that is defined as a group of metabolic diseases characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action or both, causing impaired carbohydrate, lipid and protein metabolism and increased risk of cardiovascular diseases. It is a growing health concern worldwide. Increase in sedentary lifestyle, consumption of energy-rich diets, and obesity are some of the factors resulting the rise in the number of diabetics. Diabetes is recognized as one of the leading causes of morbidity and mortality in the world. While about 2.5-7% of the world's population has been diagnosed with diabetes mellitus, it is still expected to increase in future. Despite the significant effect of the anti-hyperglycemic drugs and insulin sensitizers, side effects such as hypoglycemia at higher dose administration, low oral bioavailability due to degradation in the stomach, inactivation and digestion by proteolytic enzymes in the luminal cavity, and poor permeability across the intestinal epithelium, make it necessary to find other alternatives. This leads to an increasing demand for more study about the natural products with anti-diabetic activity and fewer side effects.

Herbal therapy has been used in patients with insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic peripheral neuropathy, and other consequences of this metabolic bolic disease. The herbal drugs are prescribed widely because of their effectiveness, fewer side effects and relatively low cost and the traditional plant medicines are used throughout the world for a range of diabetic presentations.

Therefore, the purpose of the present study was to examine the influence of the oral administration of polyherbal drug on the blood glucose concentration together with the pathological changes in pancrease, liver, kidneys, heart, lungs, stomach, large and small intestines and spleen of the alloxan-induced diabetic rats.

MATERIALS AND METHODS

Collection and authentication of the plants

The leaves and fruits of the Plants were collected from the local market of Buldhana. They were authenticated

by Head of Department of botany Shri. Shivaji Science College chikhli, Maharastra.

CHEMICALS

1. Citrullus Colocynthis: water 28.31%, Ethanol 25.22%, chloroform 3.53%, Ether 2.51%, Acetone 5.10%, Ethyl acetate 3.23%, Butanal 3.05%, Benzene 2.34%.

2. Piper Nigrum: Amino acids, steroids, triterpenoids, alkaloids, saponins, flavonoids, tannins.

3. Asparagus racemosus: Extraction of fruits, roots and leaves.

4. Cinnamomum tamala: pinene, camphene, metyl eugenol, eugenol acetate.

EXTRACTION METHOD

Citrullus Colocynthis: Colocynthis fruits were obtained from the local market. The black seeds of C. colocynthis were separated manually from the pulp of the dried fruit and were ground into powder. The powder was extracted by 1 L of hydro-ethanol mixture (80/20, v/v) for 8 h. This step was repeated for four times. The filtrate was pooled and concentrated under vacuum at a temperature, not exceeding 60°C. The alcoholic extract was stored at -20°C until being used.

Piper Nigrum: The leaves of Piper nigrum were air-dried at room temperature for four weeks after which it was grounded into fine powder. The powdered leaves (500g) were macerated in 1.5 L of absolute ethanol for 48 h. The solution was filtered with Whatmann No.4 filter paper and the filtrate concentrated to a semi-sold residue in an oven at 60oC.

Asparagus Racemosus: The roots were washed, cut into small pieces, dried in shade and coarse powdered (2000 gm) in a mixer grinder. It was extracted with soxhlet using 95% ethanol for 72 hours, concentrated on water bath (700 C), kept in oven (300 C) for drying and stored in desiccator. The yield of ethanolic extract of REAR was 26.4 gm (1.37%).

Cinnamomum Tamala: The leaves were washed in tap water and then left to dry at room temperature for 2-3 days. The dried leaves were then ground to Coarse to fine powder in a mixer and then extracted with 95% ethanol using a soxhlet apparatus for 15 hours. After filtration, the filtrate was concentrated at 65°C by a rotavapor. The concentrate was then freeze dried to yield dried powder.

EXPERIMENTAL DESIGNING

72 Healthy adult albino Wistar rats of either sex, 8-10 weeks old, weighing about 150-200 gm were used in the experiments. Animals were housed in polypropylene cages maintained under standard condition (12 hours light / dark cycle; 25 ± 3 °C, 45-65% humidity) and had free access to standard rat feed (Hindustan Lever Ltd., India) and water. All the animals were acclimatized to laboratory condition for a week before commencement of the experiment.

Acute Toxicity Study (OECD Guideline 423)

Animals were fasted prior to dosing, food but not water was withheld overnight. Following the period of fasting, the animals were weighed and test substance was administered. After the substance had been administered, food was withheld for further 3-4 hours. As a dose was administered in fractions over a period, it was necessary to provide the animals with food and water depending on the length of the period. (Ghosh MN, 1984; Turner R, 1965).

Three animals were used for each step. The dose level of the extract to be used as the starting dose was selected from one of the four fixed dose levels 500, 1000, 1500 and 2000mg/kg body weight (Lorke D, 1983). The starting dose levels such that which was most likely to produce mortality in some of the dosed animals. After administration of the test sample, the animals were observed continuously for first four hours for behavioral changes and at the end of 48 hour for mortality, if any.

Glucose Tolerance Test

Animals were fasted for 24 hours before experiment but were allowed free access to water. Fasted rats were divided into three groups of 6 animals each (WHO, 1999)

Group I - Control animals received 5% Tween 80 in distilled water at 5ml/kg b.w.p.o.

Group II - 200 mg/kg b.w. of polyherbal formulation (CPAC) p.o.

Group III - 400 mg/kg b.w. of polyherbal formulation (CPAC) p.o.

After 30 minutes of the treatment to the Groups I, II and III, 2gm/kg body weight glucose was given orally to the animals. Blood samples were collected from tail just prior to glucose administration and at 60, 120 and 180 minutes after glucose loading. The glucose levels were estimated for all the three groups by tail tipping method using Accucheck glucometer.

Effect of Formulation on Blood Glucose Levels in Alloxan Induced Diabetic Rats

30 male Wistar rats (150-200g) were made diabetic by a single i.p injection of Alloxan at a dose of 120 mg/kg i.p. after dissolving it in freshly prepared 0.1M citrate buffer (pH 4.5). The rats were maintained on 5 % glucose solution for next 24 hour to prevent hypoglycemia. Five days later blood samples were drawn from tail vein and glucose levels were determined to confirm the development of diabetes (>300mg/dl). The diabetic rats were divided into five groups, each containing six animals. Group I- Normal control rats received 5% Tween 80 in distilled water p.o.at 5 ml/kg b.w.

Group II - Diabetic control rats received 5% Tween 80 in distilled water p.o.

Group III - Diabetic rats received polyherbal formulation (CPAC) 200mg/kg b.w., p.o.

Group IV - Diabetic rats received polyherbal formulation (CPAC) 400mg/kg b.w., p.o.
Group V - Diabetic received glibenclamide at the dose of 5mg/kg b.w., p.o.
The administrations of extracts were continued for 21 days, once daily. Blood samples were collected through the tail vein on days 1, 7, 14 and 21 after drug administration and the blood glucose levels were estimated using Accu-check glucometer.

STATISTICAL ANALYSIS

Results were expressed as Mean ± SEM
Statistical analysis were performed with Graph pad prism 5 software using one way analysis of variance (ANOVA) followed by Dunnett's t test. P values less than *p<0.05, p**<0.01, p***<0.001 was considered to be statistically significant, when compared with control and standard group as applicable (Diabetes and Metabolism 1989).

RESULTS

Extraction
The dried powdered parts of the respective plants were extracted using soxhlet and /or maceration method and percentage yield of the extracts are tabulated in Table 1.

Acute Toxicity Study
Acute toxicity study of polyherbal formulation was carried out in rats. It was observed that there was no gross evidence of any abnormalities up to 4 hrs and no mortality was observed in animals up to the end of 48 hours at the maximum tested dose level of 2000mg/kg b.w. in rats. This was considered as Maximum Tolerated Dose (MTD) and thus, 1/10th of MTD i.e., 200mg/kg b.w. was taken as test dose and double the test dose i.e., 400 mg/kg b.w. was also selected for the experimental studies.

Oral Glucose Tolerance Test
The results obtained for oral glucose tolerance test with polyherbal formulation are given in Table 2 and illustrated in Graph 1. The results of the test indicated a significant increase in glucose tolerance at 60, 120 and 180 min. in extract treated group as compared to control treated group.

Effect of Formulation on different parameter in alloxan induced diabetes in rats Effect of Formulation on Blood Glucose Levels
The results obtained with polyherbal formulation on blood glucose levels are given in Table 3 and illustrated in Graph 2. The results of the test indicated a significant decrease in blood glucose levels on day 7, 14 & 21 in extract treated group as compared to control treated group.

Effect of Formulation on Total Cholesterol and Total Triglyceride Levels
The results obtained with polyherbal formulation on total cholesterol and total triglyceride levels are given in Table 4 and illustrated in Graph 3 & 4. The results of the test indicated a significant reduction in elevated total cholesterol and total triglyceride levels in extract treated group as compared to Diabetic Control group.

Effect of Formulation on HDL, LDL and VLDL Levels
The results obtained with polyherbal formulation on HDL, LDL & VLDL levels are given in Table 5 and illustrated in Graph 5, 6 & 7. The results of the test indicated a significant decrease in total LDL & VLDL levels while it increased the HDL levels in extract treated group as compared to Diabetic Control group.

Table 1: Persentage Yield of Extract.

S.No.	Plant Extract	Part Used	Solvent Used	Extraction Method	Persentage Yield of Extract
1	**Citrullus colocynthis**	Fruits	Ethanol	Soxhlation	12.7%
2	Piper nigrum	Seeds	Ethanol	Maceration	6.3%
3	Asparagus racemosus	Roots	Ethanol	Meceration	10.5%
4	Cinnamomum tamala	Leaves	Ethanol	Meceration	13.2%

Table 2: Oral Glucose Tolerance Test.

Treatment Groups	Blood Glucose Levels (mg/dL) at			
	0 min	60 min	120 min	180 min
Normal control	93.67±3.87	156.54±9.21	189.08±8.99	247.72±10.22
Polyherbal formulation CPAC 200 mg/kg b.w.,p.o.	86.78±4.92	127.39±6.87**	97.64±5.81**	90.39±4.85**
Polyherbal formulation CPAC 400 mg/kg b.w.,p.o.	91.56±4.63	119.02±7.62**	95.37±5.83**	87.65±3.91**

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Table 3: Effect of Polyherbal Formulation on Blood Glucose Levels.

Treatment groups	Blood Glucose Levels (mg/dL)on			
	Day 1	Day 7	Day 14	Day 21
Normal	98.83±4.39	103.0±3.2	109.0±2.59	111.17±3.47
Diabetic Control	300.0±11.26	320.0±6.96	333.83±5.26	343.5±4.35
Polyherbal formulation CPAC 200 mg/kg b.w., p.o.	296.33±3.04	266.66±3.64*	201.34±3.59**	176.98±3.19**
Polyherbal formulation CPAC 400 mg/kg b.w.,p.o.	285.43±43	227.0±5.4*	172.43±4.59**	129.37±4.09**
Standard Glibenclamide 5mg/kg b.w., p.o	301±11.62	261.33±9.76*	174.5±8.03**	132.17±9.08**

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Table 4: Effect of Polyherbal Formulation on Total Cholesterol and Total Triglyceride Levels.

Treatment groups	Total cholesterol levels(mg/dL)	Total triglyceride levels(mg/dL)
Normal	145.0±2.36	79.5±1.42
Diabetic Control	271.67±3.23	184.82±2.24
Polyherbal formulation CPAC 200 mg/kg b.w.,p.o.	197.5±3.25**	106.15±2.73**
Polyherbal formulation CPAC 400 mg/kg b.w.,p.o.	161.66±2.98***	97.5±2.09***
Standard Glibenclamide 5mg/kg b.w., p.o.	150.83±3.65***	83.16±2.71***

Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Table 5: Effect of Polyherbal Formulation on HDL, LDL & VLDL Levels.

Treatment groups	HDL Levels	LDL Levels	VLDL Levels
Normal	58.03±1.11	71.07±1.21	15.9±0.76
Diabetic Control	21.37±1.38	213.34±2.13	36.96±1.12
Polyherbal formulation CPAC 200 mg/kg b.w.,p.o.	57.33±0.98**	118.94±1.79**	21.23±0.98**
Polyherbal formulation CPAC 400 mg/kg b.w.,p.o.	61.08±1.37**	81.08±1.99**	19.5±0.79**
Standard Glibenclamide 5mg/kg b.w., p.o.	74.83±1.75***	59.37±1.75***	16.63±1.02***

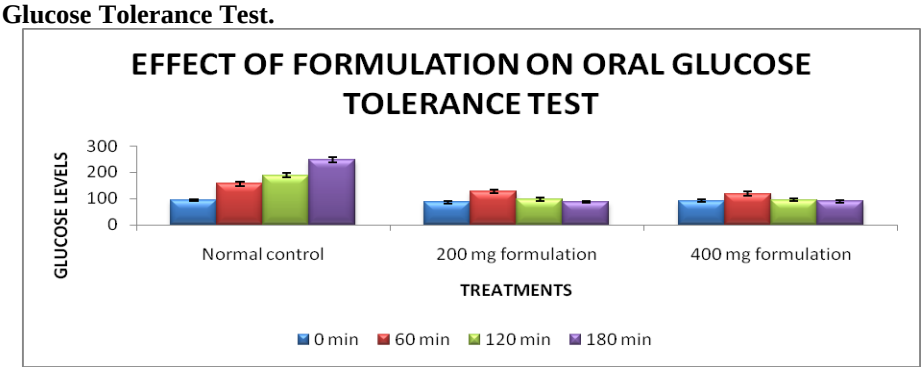
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Table 6: Effect of Polyherbal Formulation on SGPT and SGOT Levels.

Treatment groups	SGPT levels	SGOT levels
Normal	27.83±1.32	27.17±1.32
Diabetic Control	66.00±2.11	57.17±2.01
Polyherbal formulation CPAC 200 mg/kg b.w.,p.o.	40.33±1.98**	35.15±1.98**
Polyherbal formulation CPAC 400 mg/kg b.w.,p.o.	35.33±1.67***	32.66±2.34***
Standard Glibenclamide 5mg/kg b.w., p.o.	30.83±2.03***	29.03±2.76***

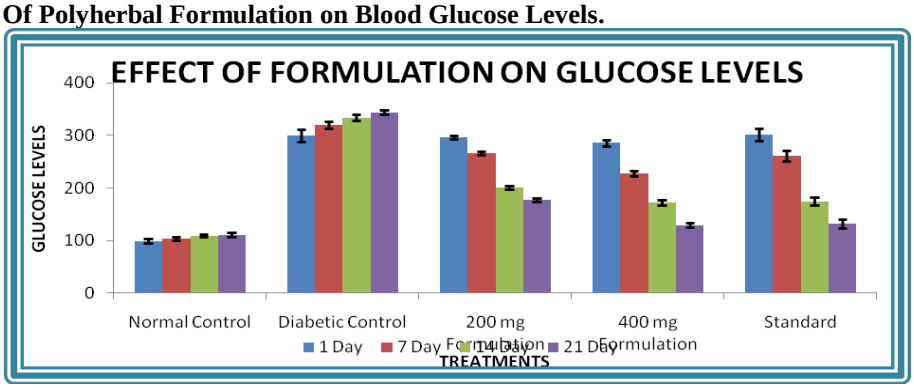
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 1: Oral Glucose Tolerance Test.



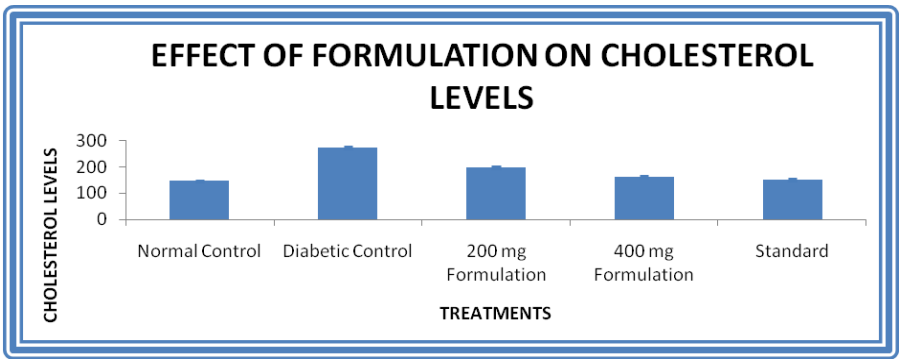
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 2: Effect Of Polyherbal Formulation on Blood Glucose Levels.



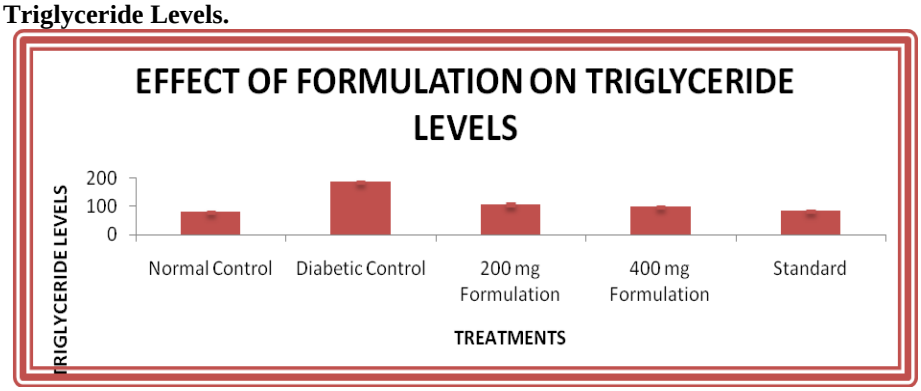
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 3: Total Cholesterol Levels.



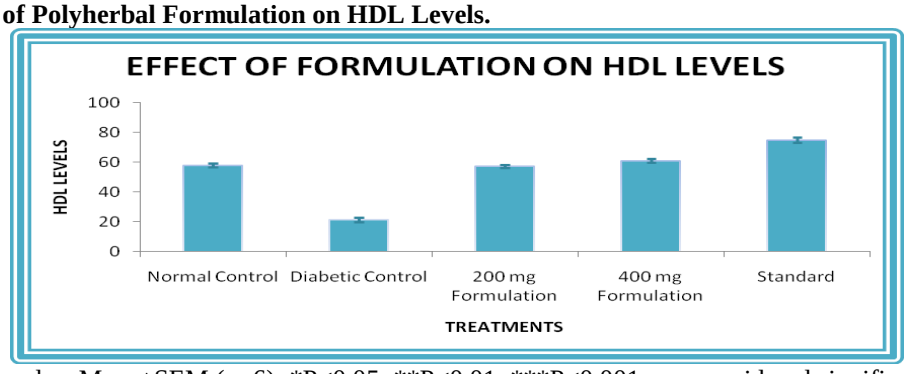
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 4: Total Triglyceride Levels.



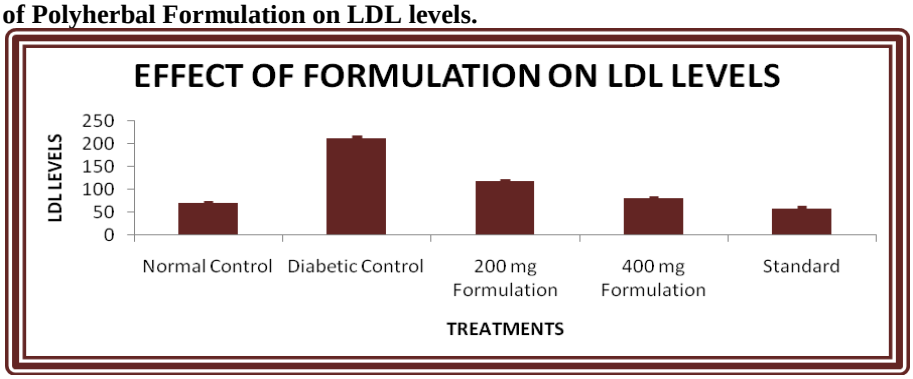
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 5: Effect of Polyherbal Formulation on HDL Levels.



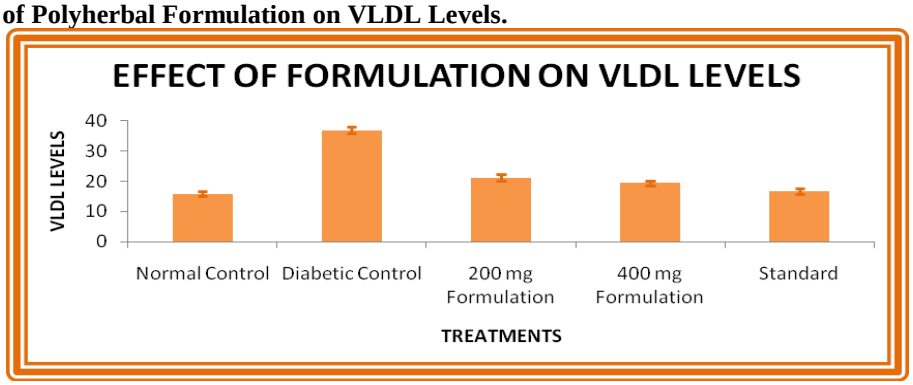
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 6: Effect of Polyherbal Formulation on LDL levels.



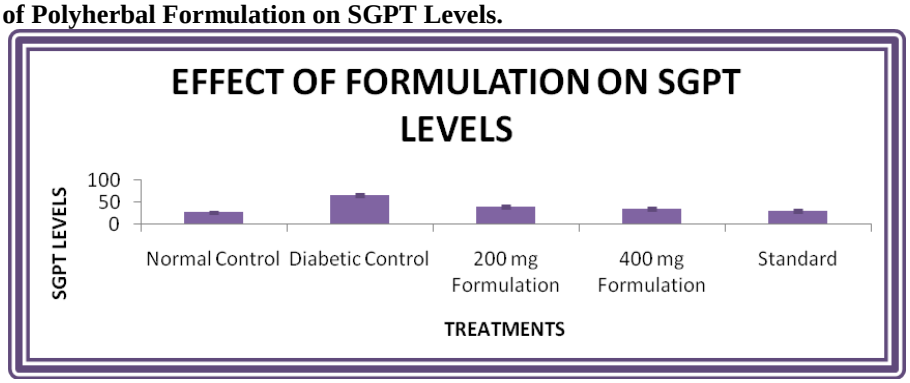
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 7: Effect of Polyherbal Formulation on VLDL Levels.



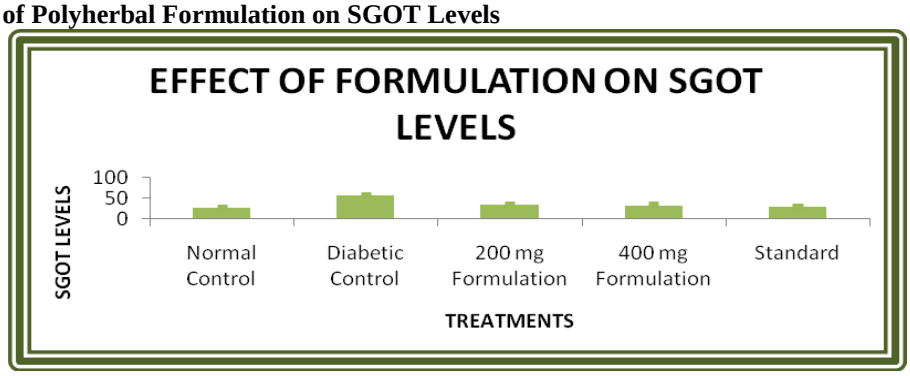
Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 8: Effect of Polyherbal Formulation on SGPT Levels.



Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Graph 9: Effect of Polyherbal Formulation on SGOT Levels



Values are expressed as Mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001 was considered significant with respect to control group using ANOVA followed by Dunnett's t-test.

Effect of Formulation on SGPT and SGOT Levels

The results obtained with polyherbal formulation on SGPT & SGOT levels are given in Table 6 and illustrated in Graph 8 & 9. The results of the test indicated SGPT & SGOT levels in extract treated group are 35.33±1.67 & 32.66±2.34 as compared to Diabetic Control group (66.0±2.11 & 57.17±2.01).

DISCUSSION

Diabetes mellitus is now recognized as one of the major killer diseases and a leading cause of death, claiming many lives world over. Oral hypoglycemic agents especially the sulphonylureas and biguanides have been commonly used in the disease management especially type II diabetes but are not without serious side effects. Consequently, attention has been focused on the use of plants and herbal remedies believed to be safer and devoid of serious side effects as alternatives in the treatment of diabetes.

The polyherbal CPAC is one of such herbal remedies prepared from the fruit of *citrullus colocynthis*, seeds of *piper nigrum*, roots of asparagus racemosus and leaves of Cinnamomum tamala used to evaluate antidiabetic activity.

The extraction value of citrullus colocynthis fruit was 12.7% w/w, seeds of *piper nigrum* were 6.3% w/w, roots of asparagus racemosus was 10.5% w/w and leaves of Cinnamomum tamala was 13.2% w/w. The Maximum Tolerated Dose (MTD) of the drug preparation was determined to be 2000 mg/kg b.w. for p.o.as there was no lethal effect at the dose. Thus, the test dose was decided as 200 mg/kg b.w.p.o. ($1/10^{th}$ of MTD) and 400 mg/kg b.w. p.o. was also decided for the experimental study.

The anti-hyperglycemic activity of the polyherbal formulation was screened using glucose tolerance test. The formulation tested for this activity exhibited significant antihyperglycemic activity at a dose level of 400 mg/kg b.w. (87.65±3.91) as compared to control (247.72±10.22) at 180 minutes. The results agree with the previous study on a polyherbal formulation i.e., Diabet containing six medicinal plants namely *Curcuma longa*, *Coscinium fenestratum*, *Strychnos potatorum*, *Tamarindus indica*, *Tribulus terrestris* and *Phyllanthus reticulants* also showed a significant antihyperglycemic effect at a dose level of 500 mg/kg b.w., p.o. at 180 minutes.

The polyherbal formulation of drug was effective in decreasing the blood glucose levels in diabetic rats at both the low and high doses significantly. The results agree with the previous study on a polyherbal formulation Okudiabet containing three herbal plants namely *Stachytarpheta angustifolia*, *Alstonia congensis* and *Xylopia aethiopica* which showed antidiabetic activity dose-dependently. There was significant increase in total cholesterol, triglyceride, LDL, VLDL, SGPT and SGOT levels and a decrease in HDL levels in alloxan induced diabetic rats compared to normal rats. Administration of polyherbal formulation at doses 200 and 400 mg/kg b.w. and glibenclamide at a dose of 5 mg/kg b.w. reversed the elevated levels of total cholesterol, triglycerides, LDL, VLDL, SGPT and SGOT significantly and increased the HDL levels significantly. 400 mg/kg b.w. dose was found to be more effective than the lower dose. The results perfectly agree with the previous study on a polyherbal formulation Dianex containing *Gymnema sylvestre*, *Eugenia jambolana*, *Momordica charantia*, *Azadira chtaindica*, *Cassia auriculata*, *Aegle marmelose*, *Withania somnifera* and *Curcuma longa* and DRY/AY/5001 containing *Gymnema sylvestre*, *Syzygium cumini*, *Pterocarpus marsupium*, *Momordica charantia*, *Emblica officianalis*, *Terminalia chebula*, *Terminalia belirica* and *shudh Shilajit.*

CPAC, a combination of fruit of *citrullus colocynthis*, seeds of *piper nigrum*, roots of asparagus racemosus and leaves of Cinnamomum tamala the present investigation showed significant antihyperglycemic and hypolipidemic activity. So, it can be used as an agent for the treatment of diabetes mellitus. However, further studies are required to be done to explore the active principles and the exact mechanism of action. The results of the present study indicate that the antidiabetic effect of the CPAC may be due to increase in insulin secretion or decrease in insulin resistance or increased glucose absorption.

CONCLUSION

The WHO has recommended and encouraged the use of alternative therapy especially in countries where access to the conventional treatment of diabetes is not adequate. The ingredients present in polyherbal formulation i.e., *citrullus colocynthis*, *piper nigrum*, *asparagus racemosus*, *Cinnamomum tamala* are widely used in various systems of medicine for a wide range of properties. In addition to antidiabetic activity, CPAC also exhibited hypolipidemic activity that may be beneficial for preventing diabetic complications. On the basis of these results, it could be concluded that CPAC, a combination of four herbal plants exerts a significant antidiabetic effect. This could be due to different types of active principles from various plants, which may have different mechanisms of action. Therefore, combination may be beneficial. However, it cannot be concluded that the combination of four plants may have synergistic or additive effect. Although, further studies are required to be conducted to investigate this hypothesis. The polyherbal formulation CPAC may be considered as safe supplementary therapy for a long term and effective management of diabetic patients. Thus, further studies can be done to identify the exact chemical constituents and mechanism of action which are responsible for the said activity.

In conclusion, the overall results of this study have clearly shown low potency (3X) or MT of *TO* to offer good protection against the deleterious renal side-effects

of gentamicin. Although the exact nephroprotective mechanism(s) of *TO* were not investigated in the present study, this could constitute an area of future studies. So, These strategies of treatment will be suitable/safe for clinical practice. The present findings coincide with those of earlier studies, which reported that, plants present in.

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