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"Evaluation of Hypoglycemic Activity of Bark Extracts of *Clerodendrum phlomidis*."

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ABSTRACT:

Background: *C. phlomidis* is an important and well-known medicinal plant used in the treatment of smallpox, inflammation, coryza, scrotal enlargement, syphilitic, and postnatal complaints. The roots are used to treat measles, gonorrhea, and diabetes. The present study was performed to explore the hypoglycaemic effect of hydroalcoholic extract of bark of *C. phlomidis* in alloxan-induced diabetic rats.

Materials and methods: Hypoglycemic potential was evaluated through the alloxan-induced Diabetes rats model at 120 mg/kg/p.o doses of the hydroalcoholic extracts of *C. phlomidis* bark using Glibenclamide as a standard drug. Apart from this, we have evaluated parameters like HbA1C%, Serum creatinine, Blood urea, Uric acid, Serum triglycerides, Serum cholesterol, Serum HDL, Serum LDL, Serum VLDL levels, SGOT, SGPT, Serum bilirubin total, Serum bilirubin direct, and Serum bilirubin, etc.

Results: plant exhibited dose-dependent Hypoglycemic effect with maximum activity observed at 120 mg/kg/ b.w/ p.o. The result of the alloxan-induced diabetic model depicted a significant decrease in blood glucose levels at different time intervals as compared to the positive control group. The hydroalcoholic extract was found to be effective to stimulate the pancreatic β cells to secrete insulin after an overdose of glucose which maintains a normal blood glucose level. Moreover, the phytochemical analysis revealed the presence of phytochemicals such as Flavonoids, Alkaloids, Phenolic compounds, Tannins, Terpenoids, Glycosides, Saponins, Carbohydrates, Amino acids, and Proteins.

Conclusion: By deeply analyzing the obtained results and data our research work supports the traditional use of *C. phlomidis* bark as a potential hypoglycemic agent that may be proposed for diabetes treatment.

Keywords: Hypoglycemia, *C. phlomidis*, alloxan, Glibenclamide, Flavonoids.

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance, and sometimes ketonemia. A widespread pathological change has been seen like thickening of the capillary basement membrane, increase in vessels wall matrix, and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy, and peripheral vascular insufficiency.[1] Many indigenous medicinal plants are useful to successfully manage diabetes. Synthetic drugs are either too expensive or have undesirable side effects or contraindications. Therefore, the search for more effective and safer hypoglycemic agents has continued to be an area of active research.[2] *C. phlomidis* is a plant belonging to the family Lamiaceae. *C. phlomidis* is an important and well-known medicinal plant extensively used in the Ayurveda and Siddha systems of medicine for the treatment of various ailments. The popular therapies include inflammation, diabetes, nervous disorder, asthma, rheumatism, digestive disorders, and urinary disorders as well as a bitter tonic[3]. The alcoholic and aqueous extracts of leaves of *C. phlomidis* were reported active as an analgesic, anti-diarrhoeal, anti-plasmodial, hypoglycemic, minor tranquilizers, anti-asthmatic, antifungal, nematicidal, anti- amnestic, and anti-arthritic. The decoction of fresh roots is also given orally to cure gonorrhea and to cure measles.[4,5] The various phytoconstituents reported in *C. phlomidis* are monoterpene and its derivatives, sesquiterpenes, diterpenoid, triterpenoids; flavonoid and

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glycosides, phenylethanoid glycosides, steroid and steroid glycosides, cyclohexylethanoids, anthraquinones, and cyanogenic glycosides. [6,7,8]

II. MATERIAL AND METHODS-

Collection of the plant material: Plant material *C. phlomidis* was collected from the CAZRI, Jodhpur (Central arid zone research institute). The whole plan was identified and authenticated from BSI, Jodhpur. A voucher specimen (BSI/AZRC/Tech./I.12014/2021-22 (PI. Id.) 507) of the plant was deposited in the laboratory.

Extraction of plant part:
The bark of *C. phlomidis* was dried under shade for the next 15 days and crushed to a coarse powder. The powder of *C. phlomidis* (bark) was extracted with 95% ethanol & water solvent successively by using the soxhlet apparatus. The extract was concentrated in the water bath and finally reduced to dryness. [9]

Phytochemical screening of the extracts:
The obtained extracts of *C. phlomidis* bark were screened for the presence of various phytoconstituents in them like the alkaloids, flavonoids, tannins, glycosides, saponins, and steroids.[10] The various phytochemical tests and reagents that were used for the phytochemical investigation are given below in table-1

Table 1 - Qualitative chemical examination of the ethanolic extract of the root of *C. phlomidis*[10,11,12]

S. No.	Name of chemical test	Result
1.	**Test for carbohydrate**	
	Molish test	+ Ve
	Fehling test	+ Ve
2.	**Test for protein**	
	Millions test	-Ve
3.	**Test for fats and oil**	
	Solubility Test	• -Ve
	Filter paper test	-Ve
4.	**Test for terpenoids**	+ Ve
5.	**Test for anthraquinones**	-Ve
6.	**Test for phytosterols**	
	Salkowaski test	+ Ve
	Lieberman-Burchard test	+ Ve
	Sulfur test	+ Ve
7.	**Test for alkaloids**	
	Mayer's reagent test	-Ve
	Dragendroff's test	-Ve
	Hager's test	-Ve
	Wagner's test	-Ve
8.	**Test for glycoside**	
	Legal test	-Ve
9.	**Test for flavonoids**	
	Shinoda test	+ Ve
10.	**Test for phenols**	+ Ve
11.	**Test for tannins**	+ Ve

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12.	**Test for saponins**	
	Foam test	-Ve

Experimental animals:

Healthy male Wister rats, weighing about 150-200g were kept in polypropylene cages. The animal was rared in the animal house in a conducive environmental situation i.e. temperature (25±2˚C), humidity (45-50%), and 12 hrs dark and light cycle. The animals were fed ad libitum with a normal laboratory chow standard pellet diet. The animals were allowed to be acclimatized for the next 7 days before commencing the experiments. All the studies were conducted following the Animal Ethical Committee on the Institute (No.1719/PO/Ere/S/13/CPCSEA). The protocol of the study was prepared and approved by IAEC.

Acute oral toxicity (AOT):

Healthy female albino Wistar rats weighing 180-200 grams were employed in acute oral toxicity studies and were performed according to guideline no. 423 of the Organization for Economic Co-operation and Development (OECD)[13]. Each group of animals received a dose of 2000 mg/kg. The treated animals were monitored for clinical signs like tremors, convulsions, lethargy, coma mortality, and general behavior for the next 14 days after dosing. No death was observed till the end of the study.

Table 2- Acute oral toxicity signs [14,15]

S. No.	Clinical signs	Observed sings
1.	Tremors	Not observed
2.	Convulsion	Not observed
3.	Salivation	Not observed
4.	Diarrhea	Not observed
5.	Lethargy	Not observed
6.	Coma	Not observed
7.	Mortality	No mortality was observed

Drugs and chemicals:

The standard drug Glibenclamide was obtained from Sanofi Indian Ltd. Ankleshwar Maharashtra India and Alloxan monohydrate was obtained from Loba Chemie Ltd. Mumbai India.

Assessment of the Hypoglycemic activity:

The animals were divided in about five groups having six animals in each (n=6), with group one was served as positive control (Normal Saline p.o), group two was negative control (Alloxan 120mg/kg I.P), group three received (Alloxan + Glibenclamide 120mg/kg + 2.5mg/kg,I.P. + Oral), group four received (Alloxan + Extract 120mg + 100mg/kg, I.P. + Oral) and group five received (Alloxan + Extract 120 + 200mg/kg, I.P. + Oral). diabetes was induced in male Wistar rats by intraperitoneal injection of 120 mg/ kg body weight of alloxan monohydrate (freshly prepared solution of alloxan in phosphate buffer with pH 4.5). Rats were orally treated with 20% glucose solution (5-10 ml) after 6 hrs of intra-peritoneal alloxan injection, The rats having blood glucose levels in the range of 200-300 mg/dl were included in the study. The animals were tested for evidence of diabetes by the estimation of their blood glucose level by using a Glucometer. Each group of rats received their respective doses in the morning and the treatments were continued for the next 15 days. On the 15th day of the study blood samples were collected by tail cutting method at different time intervals (0, 1, 2, 4, 6 hrs), and blood glucose level was monitored.

Statistical analysis:

All data were expressed as mean ± SEM(n=6 per group). ANOVA followed by Dunnett's test was used for statistical analysis. represent statistical significance vs diabetic control rats at $p \leq 0.05$ and ** represent statistical significance vs diabetic control rats at $p \leq 0.01$.

III. RESULTS AND DISCUSSION:

Phytochemical screening of the extracts revealed the presence of carbohydrates, terpenoids, phytosterols, flavonoids, phenols, and tannins but not the presence of proteins, fats and oils,

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anthraquinones, alkaloids glycosides, and saponins. In the case of acute oral toxicity study, the extracts do not produce any toxicity or mortality in animals and the highest tolerable dose was 2000 mg/k.g/ b.w / p.o.

The effect of the extracts and drugs seen on various parameters are listed below

Triphasic response of alloxan in diabetic rats: Induction of diabetes in rats by using alloxan has been described as a useful experimental model for studying the effect of hypoglycaemic agents. Alloxan evokes a sudden rise in insulin secretion in the presence or absence of glucose. The alloxan action in the pancreas proceeds by its rapid destruction of pancreatic β-cells. After injecting alloxan into the albino Wistar rats, the blood glucose level of each rat was measured with a glucometer after 0, 2, 48, and 72 hrs of alloxan administration. The triphasic response was observed in different groups of rats after receiving alloxan at different time intervals is depicted in table -3

Table -3 Triphasic response observed in alloxan-induced diabetic rats

Groups	BGL (mg/dl) at different time interval			
	O hr	2 hr	48 hr	72 hr
Normal	79.9±1.80	87.1±1.96	84.1±2.75	80.5±1.36
DCG	77.1±1.86	71.1±	124.8±	374.1±10.2
SGG	77.2±1.73**	68.6±1.40**	121.8±3.12**	380.1±3.10**
CPE 100	80.4±1.37*	70.1± 1.70*	116.0±4.69*	382.03±4.50*
CPE 200	81.08±1.66**	69.95± 2.08**	110.2±3.23**	376.6±2.69**

2 hrs of injection of alloxan caused a sudden drop in blood glucose level (BGL) after that BGL was significantly increased at 72 hrs of alloxan administration. The BGL indifferently treated rats significantly ($p<0.01$) decreased 24 hrs of injection of alloxan followed by significantly increased at 72 hrs of alloxan administration. It indicates that alloxan produced a triphasic response due to the destruction of β-cells.

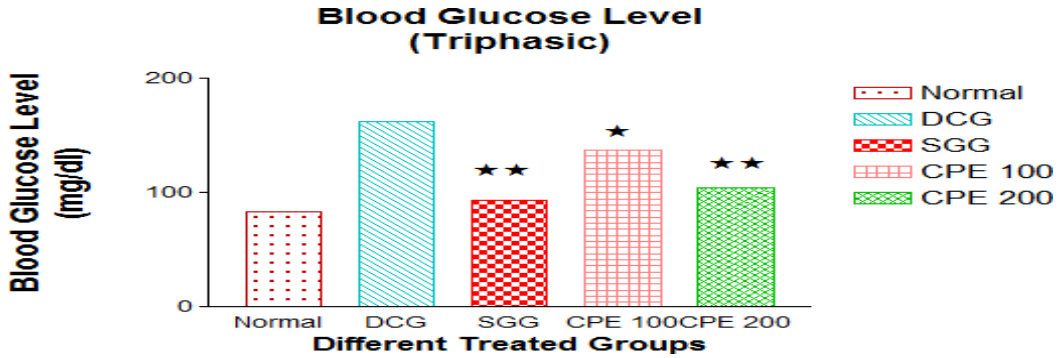

Figure -1- Effect of alloxan on blood glucose level of albino Wistar rat (Triphasic)

Oral glucose tolerance test: OGTT test was performed in normal rats (Albino Wistar rat) of either sex weighing from 200 to 300 gm. The animals were divided into 4 experimental groups each containing 6 animals each in a group. The animals fasted overnight before the study. During the treatment, Group I served as control and received a 2% acacia solution. Group II served as standard and received a 0.5 mg/kg dose of glibenclamide. Groups III and IV received 100 and 200 mg/kg doses of ethanol extract respectively. After 60 min of standard and extract administration, all animals were given 2 g/kg body weight of glucose. Immediately blood samples were collected every 0, 30, 60, 90, and 120 min from the tail vein and blood glucose levels were checked using a blood glucometer.

Table -4- Effect of hydroalcoholic extract of the root of *C. phlomidis* on oral glucose tolerance test

Groups	0 min	30 min	60 min	90 min	120 min

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Control	97.3±6.83	96.6±6.12	136.8±6.61	148.2±6.36	116.5±6.12
SGG	85±3.72**	86±4.88**	97±4.87**	115±5.24**	90±4.16**
CPE 100	91±3.93*	95±4.45*	106±2.50*	120±2.31*	104±1.16*
CPE 200	80±3.79**	79±4.67**	112±4.29**	123±43.7**	114 3.32**

Administration of glucose 2 g/kg in different treated groups of rats caused a significant elevation in blood glucose levels at different time intervals (0, 30, 60, 90, and 120 min) when compared to the positive control group. Treatment with glibenclamide (0.5 mg/kg) significantly lowered the blood glucose level at different time intervals in comparison to positive control rats. Groups treated with hydroalcoholic extract at low and high-dose levels (100 and 200 mg/kg) respectively, showed a significant decrease in blood glucose level at different time intervals as compared to the positive control group. The hydroalcoholic extract was found to be effective to stimulate the pancreatic β cells to secrete insulin after an overdose of glucose which maintains a normal blood glucose level.

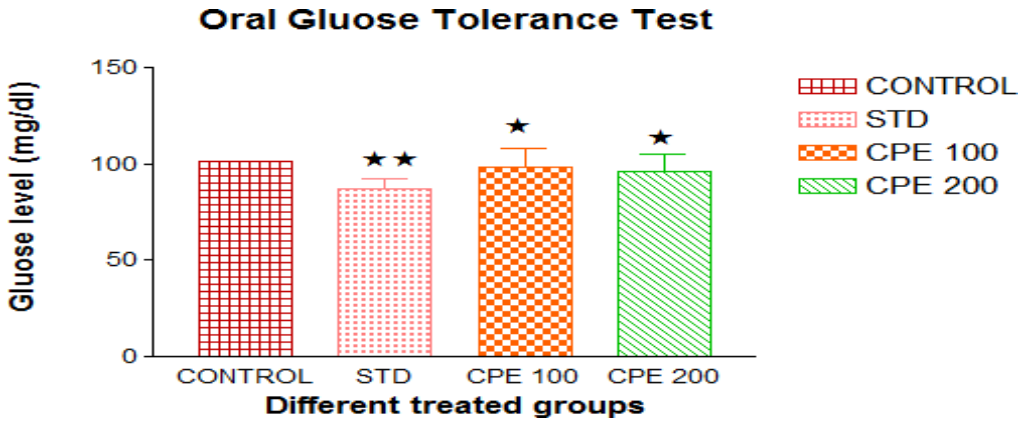

Figure 2- Effect of hydroalcoholic extract of the root of *C. phlomidis* on oral glucose tolerance test

Acute hyperglycaemic activity: The different groups of rats received their respective doses as mentioned above in the study design. The results of BGL of different treated groups of rats on days 1st, 7th, and 15th are depicted in tables no. 5, 6, and 7 respectively

Table 5- Effect of hydroalcoholic extract of the root of *C. phlomidis* in alloxan-induced diabetic rats on the first day of the treatment at different time intervals.

Acute hyperglycaemic study 1st day					
Groups	Blood Glucose Level (mg/dl) at a different time interval (Mean± SEM)				
	0 hr	1 hr	2 hr	4 hr	6hr
NORMAL	97.8±6.55	97.2±6.4	97.2±6.85	97.1±6.36	97.1±6.33
DCG	312±15.7	321±13.4	320±2.4	314±13.1	317±1.31
SGG	307±34.7**	276±30**	150±10.3**	144±11.7**	225±20.1**
CPE 100	260±21.4*	171±4.08*	133±4.33*	106±3.06*	123. 5.54*
CPE 200	304±47.6*	290±45.6*	284±45.1*	281±44.1*	287±45.4*

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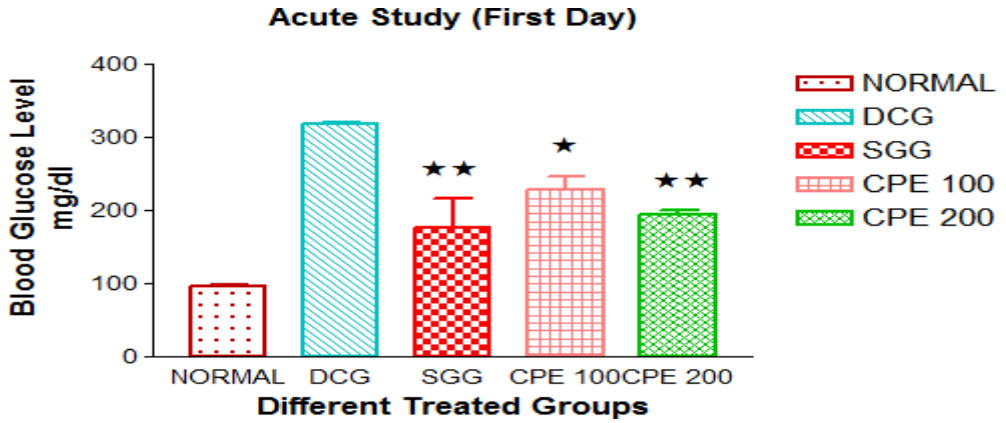

Figure 3- Effect of hydroalcoholic extract of bark of *C. phlomidis* in alloxan-induced diabetic rats on the first day of the treatment at different time intervals

Table 6- Effect of hydroalcoholic extract of the root of *C. phlomidis* in alloxan-induced diabetic rats on the 7th day of the treatment at different time intervals.

Acute hyperglycaemic study 7th day					
Groups	Blood Glucose Level (mg/dl) at a different time interval (Mean± SEM)				
	0 hr	1 hr	2 hr	4 hr	6hr
NORMAL	97.8±6.55	96.6±6.12	97.8±6.61	97.1±6.36	96.5±6.12
DCG	296±14.4	295 ±4.3	293±10.4	294±10.4	293±10.1
SGG	188±5.08**	160±7.22**	153±3.48**	146±5.03**	150±3.61*v
CPE 100	201±15.9*	149±5.61*	109±3.72*	93±3.97*	97.8±2.13*
CPE 200	280±6.22**	280±5.78**	281±6.19**	283±4.76**	283±5.20**

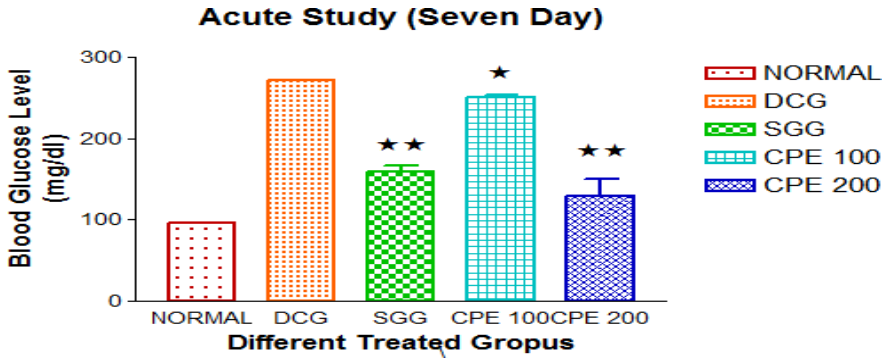

Figure 4- Effect of hydroalcoholic extract of the root of *C. phlomidis* in alloxan-induced diabetic rats on the 7th day of the treatment at different time intervals.

Table 7- Effect of hydroalcoholic extract of the root of *C. phlomidis* in alloxan-induced diabetic rats on the 15th day of the treatment at different time intervals.

Acute hyperglycaemic study 15th day					
Groups	Blood Glucose Level (mg/dl) at a different time interval (Mean± SEM)				
	0 hr	1 hr	2 hr	4 hr	6hr
NORMAL	97.3±6.83	96.6±6.12	96.8±6.61	97.2±6.36	96.5±6.12
DCG	283±28.8	284±22.4	286±21.5	287±20.1	288±20.2
SGG	145±3.72**	138±4.88**	137±4.87**	135±5.24**	140±4.16**

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CPE 100	135±3.93*	112±4.45*	106±2.50*	99.1±2.31*	104±1.16*
CPE 200	280±13.7*	280±14.6*	282±14.2*	283±13.7*	284 13.2*

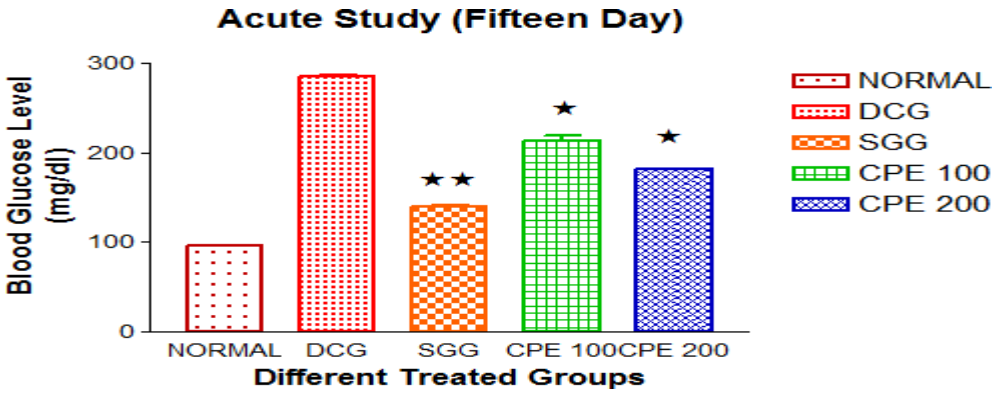

Figure 5- Effect of hydroalcoholic extract of the root of *C. phlomidis* in alloxan-induced diabetic rats on the 15th day of the treatment at different time intervals.

The effect of hydroalcoholic extract of bark of *C. phlomidis* on BGL at different time intervals is depicted in the table (4-6). DCG of rats showed a significant ($p \leq 0.01$) increase in BGL as compared to NCG. The result of the CPE 200 treated group of rats showed a significant ($p \leq 0.01$) effect in reducing the BGL at different time intervals as compared to diabetic control rats. However, CPE 100 treatment did not show a significant reduction in BGL. The maximum hypoglycaemic effect of the CPE 200 treated rats was observed at 4 hr of dosing, it indicates that the CPE 200 provides good glycaemic control in diabetic rats for a longer duration of action. However, the effect of CPE in diabetic rats did not work in a dose-dependent manner.

DCG- Diabetic control group, BGL- Blood glucose level, CPE- C. phlomidis extract, SGC-Standard glibenclamide control.

Estimation of biochemical parameters:

Determination of percentage glycosylated hemoglobin (HbA1C%) -EDTA- blood samples that were collected at the end of the study from each treated group of rats were subjected to HbA1C % estimation at the end of the study (15th day) as depicted in figure -6

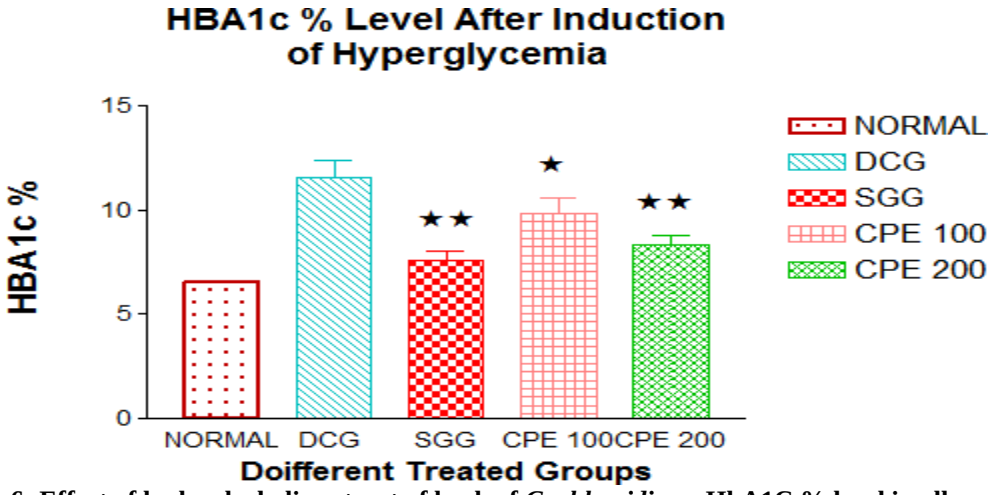

Figure 6- Effect of hydroalcoholic extract of bark of *C. phlomidis* on HbA1C % level in alloxan-induced diabetic rats

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Evaluation of renal cardiac and liver functions: EDTA blood samples that were collected at the end of the study from each treated group of rats were subjected for Blood Urea, Serum Creatinine, Serum Uric Acid, Serum Triglyceride, Serum Cholesterol, Serum HDL(Direct), Serum LDL(Direct), Serum VLDL level estimation at the end of the study(15th day) the result is depicted in figure 6

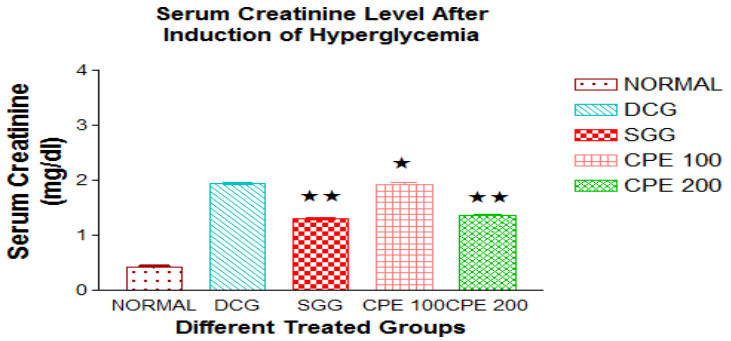

Figure 7-Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum creatinine level in alloxan-induced diabetic rats

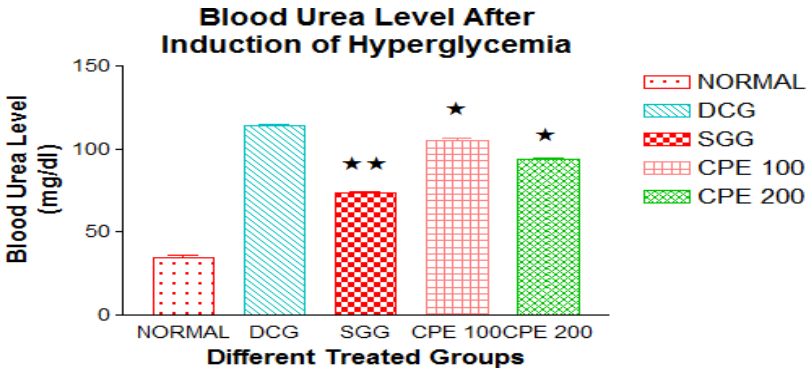

Figure 8- Effect of hydroalcoholic extract of bark of *C. phlomidis* on blood urea level in alloxan-induced diabetic rats

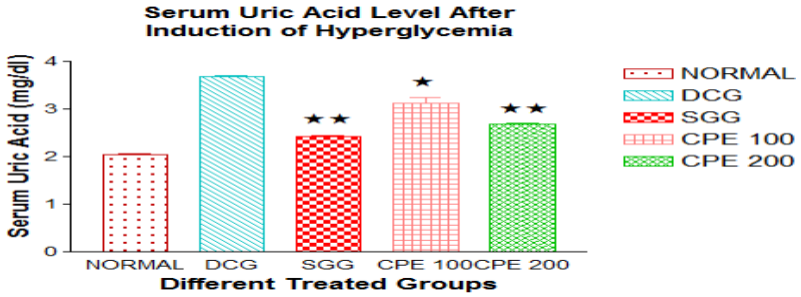

Figure 9- Effect of hydroalcoholic extract of bark of *C. phlomidis* serum uric acid level in alloxan-induced diabetic rats.

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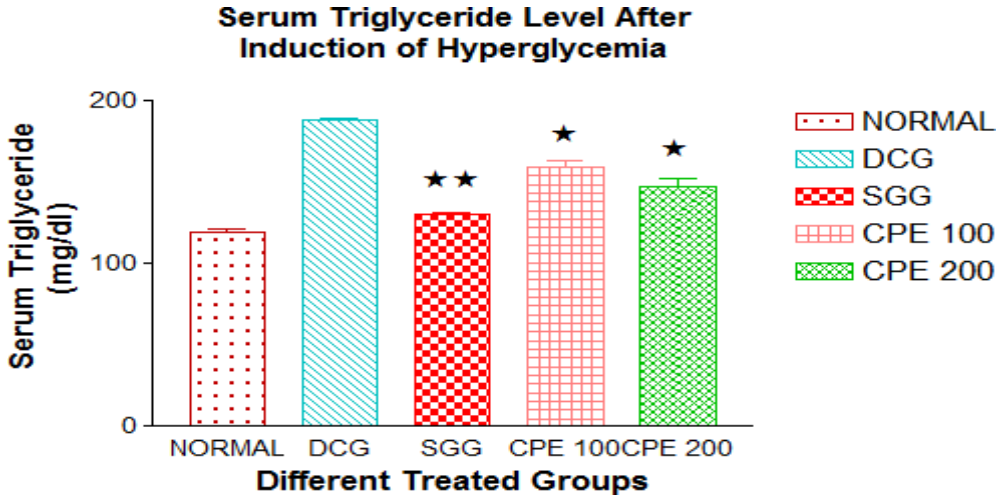

Figure 10- Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum triglyceride level in alloxan-induced diabetic rats

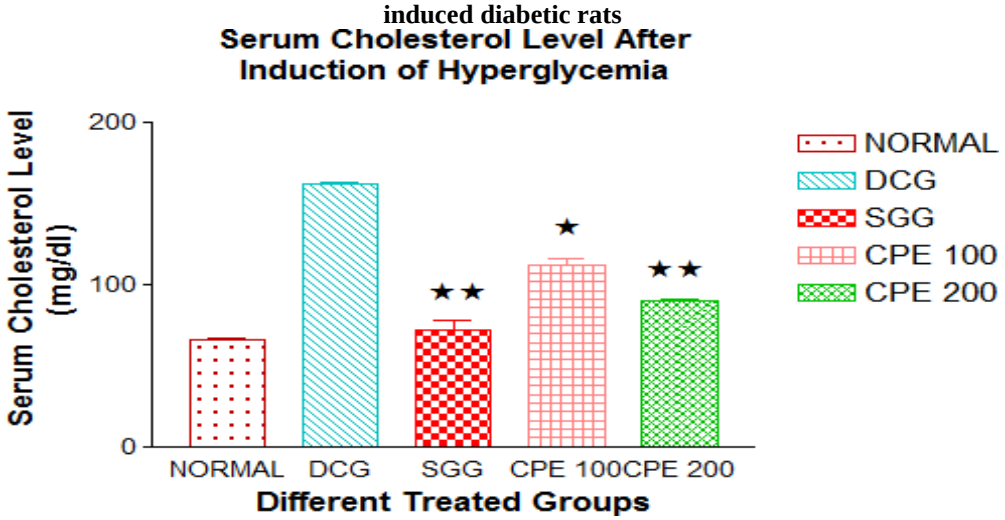

Figure 11- Effect of hydroalcoholic extract of bark of *C. phlomidis* on the serum cholesterol level in alloxan-induced diabetic rats

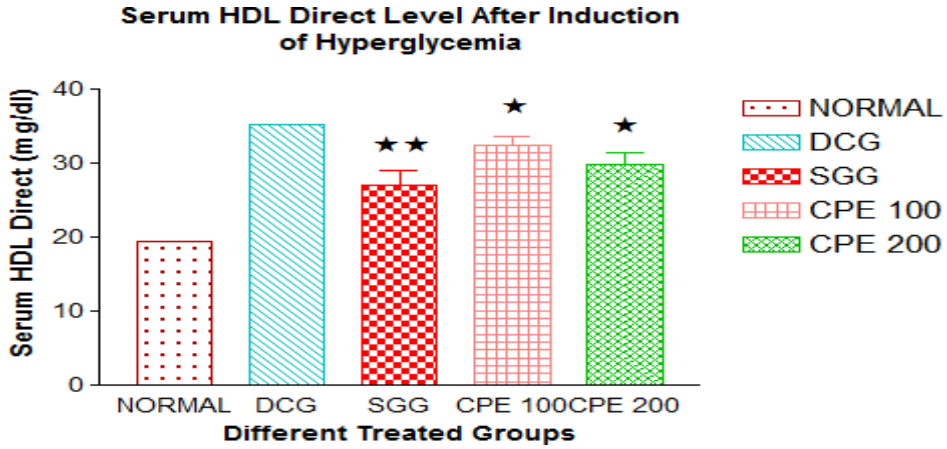

Figure No. 12 Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum HDL (Direct) level in alloxan induced diabetic rats

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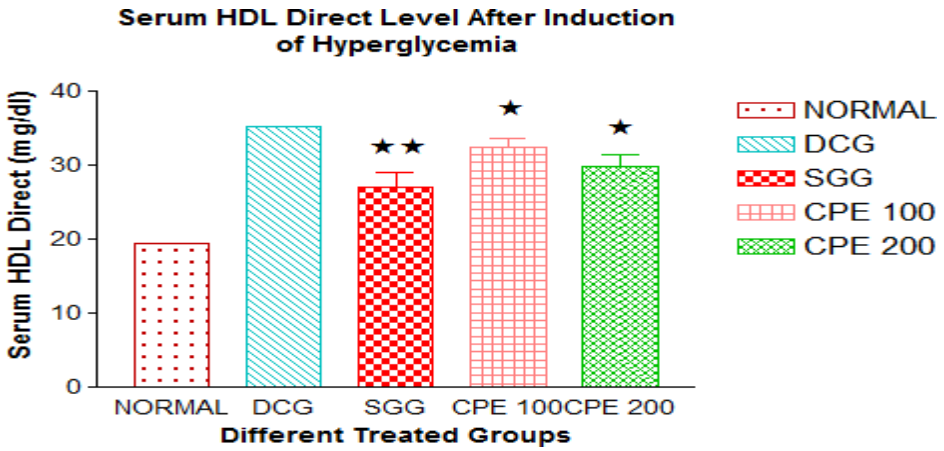

Figure 13 Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum LDL (Direct) level in alloxan-induced diabetic rats

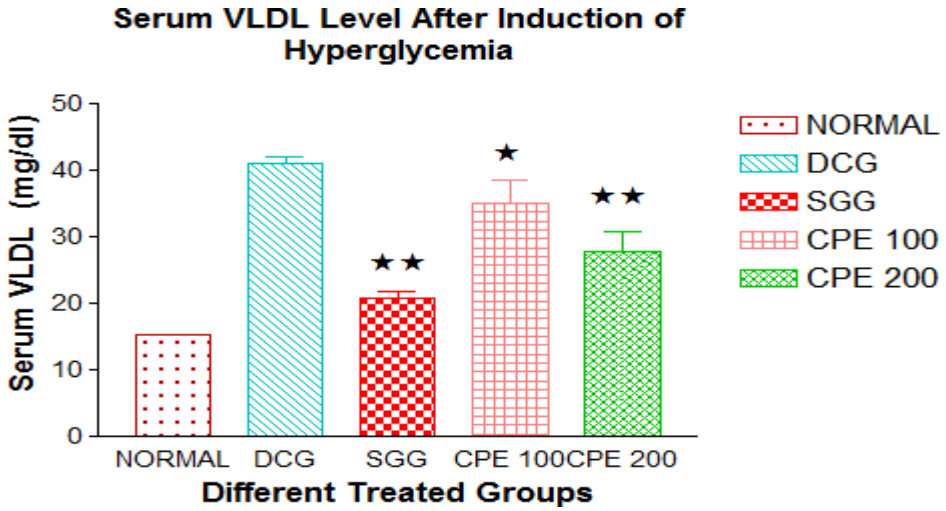

Figure 14- Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum VLDL level in alloxan-induced diabetic rats

Estimation of liver function test: Assay of the blood maker enzyme which includes Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), and Bilirubin (Total, Direct and Indirect) were done in each treated group of rats. The results of liver function tests of different treated groups of rats are depicted in figure

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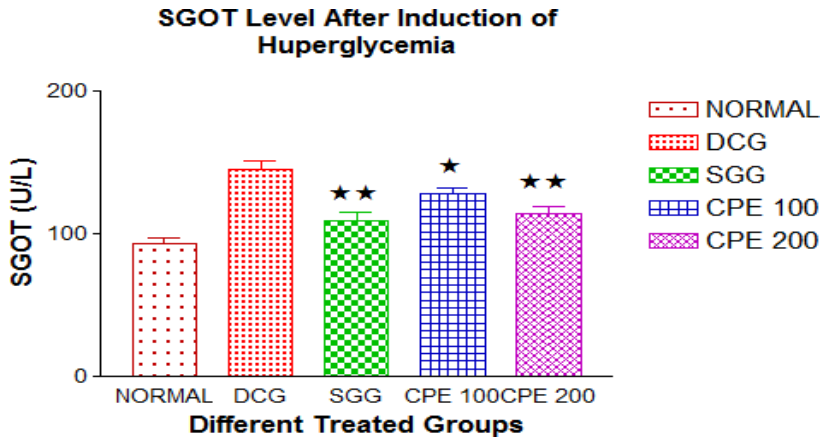

Figure 15- Effect of hydroalcoholic extract of bark of *C. phlomidis* on SGOT level in alloxan-induced diabetic rats

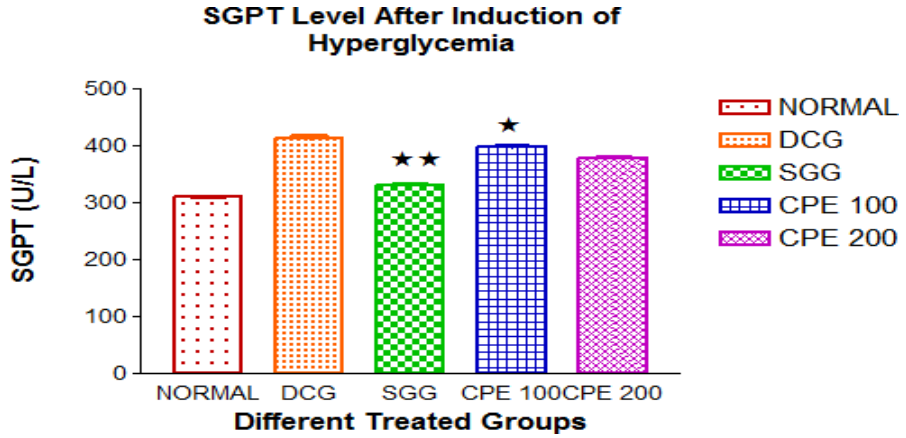

Figure 16- Effect of hydroalcoholic extract of bark of *C. phlomidis* on SGPT level in alloxan-induced diabetic rats

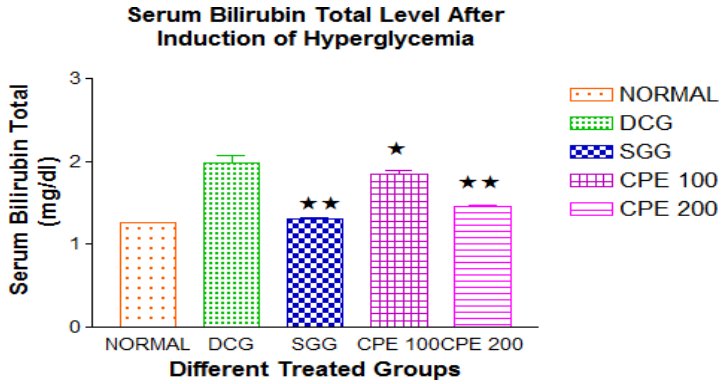

Figure 17- Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum bilirubin total level in alloxan-induced diabetic rats.

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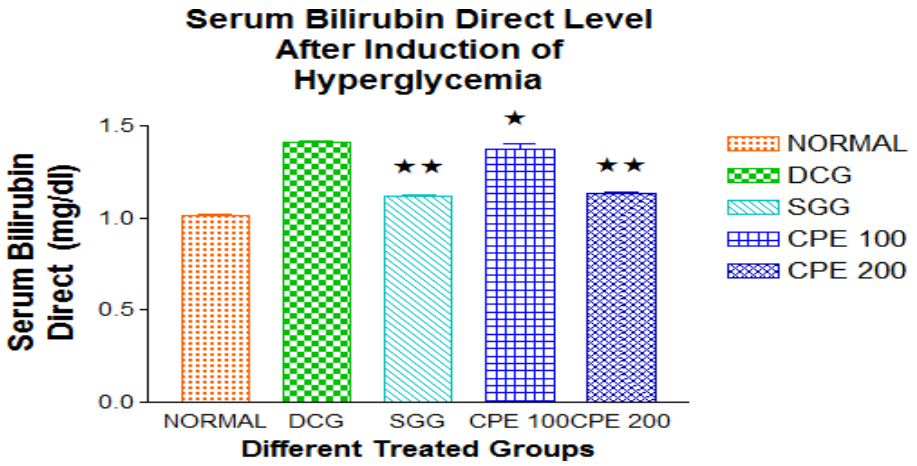

Figure 18- Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum bilirubin direct level in alloxan-induced diabetic rats

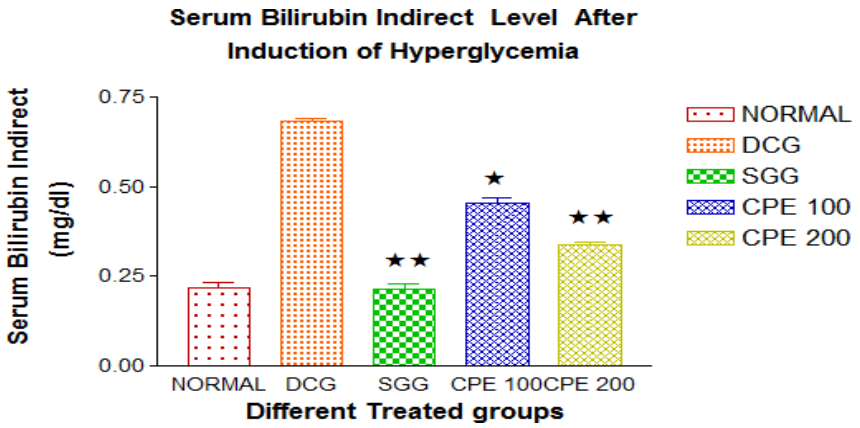

Figure 19- Effect of hydroalcoholic extract of bark of *C. phlomidis* on serum bilirubin indirect level in alloxan-induced diabetic rats.

Table 8- HbA1C%, Serum creatinine, Blood urea, Uric acid, Serum triglycerides, and levels of different treated groups of diabetic rats (Measured on the 15th day of study)

Groups	HbA1C %	Serum creatinine (mg/dl)	Blood-urea (mg/dl)	Uric acid (mg/dl)	Serum triglycerides (mg/dl)
NCG	5.91±0.37	2.58±0.007	3.66±0.0051	2.75±0.0088	8.83±0.03
DCG	14.89±0.80	11.63±0.012	4±1.154	3.66±0.0088	7.33±0.01
SGG	6.76±0.32**	7.78±0.013**	7.33±0.843**	3.43±0.0076**	5.16±0.08**
CPE 100	8.73±0.32*	1.75±0.014*	4.83±1.66*	2.76±0.0054*	5.16±0.02*
CPE 200	7.88±0.37**	1.37±0.011**	3.5±0.991**	3.19±0.038**	6.54±0.15**

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Table 9- Serum cholesterol, Serum HDL, Serum LDL, and Serum VLDL levels of different treated groups of diabetic rats (Measured on the 15th day of study)

Groups	Serum cholesterol	Serum HDL	Serum LDL	Serum VLDL
NCG	66.5±0.76	22.33±1.11	29.66±0.88	15.33±0.76
DCG	161.66±1.14	20.5±1.17	95.66±1.14	41±1.06
SGG	90.33±0,84**	21.16±1.10**	32.5±0.88**	20±1.01**
CPE 100	112.16±0.94*	19.33±0.98*	65.6±1.25*	29±0.68*
CPE 200	77.33±0.91**	22.5±0.99**	46.83±1.22**	2.66±1.08**

Table 10 SGOT, SGPT, Serum bilirubin total, Serum bilirubin direct and Serum bilirubin indirect levels of different treated groups of diabetic rats (Measured on 15th day of study)

Group	SGOT	SGPT	Serum Bilirubin Total	Serum Bilirubin Direct	Serum Bilirubin Indirect
NCG	93.33±3.34	365±7.35	1.25± 0.008	1.02±0.08	1.028±0.008
DCG	145.5±5.773	410±7.96	2.09±0.021	1.40±0.009	1.40±0.009
SGG	109.5±6.05**	380.16±6.1**	1.31±0.007**	1.13±0.10**	1.13±0.010**
CPE 100	124.16±5.12*	400±6.91*	1.46±0.009*	1.13±0.09*	1.35±0.009*
CPE 200	113.83±5.67**	384±4.86**	1.74±0.011**	1.25±0.10**	1.25±0.013**

CPE 200 treated group of rats showed significant ($p \leq 0.01$) improvement in the biochemical parameter as compared to untreated DC rats. The CPE 200 mg/kg dose of *C. phlomidis* showed significant improvement in the level of various biochemical parameters as compared to the CPE 100 mg/kg dose of *C. phlomidis*. It indicates that CPE extract did not show its effect in a dose-dependent manner.

HbA1C % level is commonly used to measure the glycaemic control of patients with Diabetes Mellitus. CPE 200 treated group of diabetic control rats showed significant reduction ($p \leq 0.01$) in HbA1C% level as compared to diabetic control rats. This may be due to the improvement in the glycaemic control mechanisms via one of the mechanisms for controlling BGL i.e. Increase in insulin secretion, decrease in insulin resistance and decrease in hepatic glucose production.

CPE 200 treatment in diabetic rats showed a significant reduction in LDL, VLDL, TG, and total cholesterol as compared to diabetic control rats. This effect of normalization of lipids levels in diabetic rats treated with CPE 200 may due to its stimulatory effect on insulin secretion from ruminant pancreatic β-cells or may be due to the uptake of glucose by peripheral tissues.

IV. CONCLUSION:

95% Ethanol water bark extract of *C. phlomidis* contain carbohydrates, terpenoids, phytosterol, flavonoids, phenols, tannins compounds, and Flavanoids. In the above result and discussion, it is concluded that *C. phlomidis* bark extract was found to show the remarked hypoglycemic property in the experiment carried out which summarizes that this research done pharmacologically supports the folkloric and the traditional ancient use of *C. phlomidis* bark in the supportive treatment and the management of diabetes.

The present study requires more study to know the exact and proper mechanism but presently it was concluded that *C. phlomidis* bark has flavanoids like quercetin, daidzein, silymarinapigenin, and genistein, which have hypoglycemic properties, but some specific mechanisms and some novel phytochemicals responsible for the same potential

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CONFLICT OF INTEREST:
The authors declare no conflict of interest.

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