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PREPARATION AND EVALUATION OF ANTIDIABETIC ACTIVITY OF A NOVEL ORAL POLY-HERBAL FORMULATION: A PROMISING APPROACH FOR DIABETES MANAGEMENT

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ABSTRACT
This study focuses on the preparation and evaluation of the antidiabetic activity of a novel oral polyherbal formulation. The formulation consists of Neem, Tulsi, Fenugreek, Turmeric, and Cinnamon, which were collected, dried, and extracted using different solvents. The physicochemical properties of the powdered herbs were determined, including moisture content, total ash value, acid-insoluble ash, water-soluble ash, alcohol-soluble extractive value, and water-soluble extractive value. Preliminary phytochemical evaluation of the polyherbal extracts was conducted to identify the presence of compounds such as alkaloids, glycosides, tannins, resins, flavonoids, steroids, amino acids, proteins, carbohydrates, fats & oils, phenols, diterpenes, and saponins. An acute toxicity study was performed to determine the safety of the polyherbal formulation, and no morbidity or mortality was observed at a dose of 2000mg/kg body weight. Diabetes was induced in rats using streptozotocin, and the rats were divided into different treatment groups, including a normal control group, a toxic control group, a standard control group receiving glibenclamide, and treatment groups receiving different doses of the polyherbal formulation. The rats were treated orally for 28 consecutive days, and their body weight variations were monitored weekly. Blood samples were collected at regular intervals to estimate blood glucose levels, and at the end of the experiment, further biochemical analysis was conducted. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's t-test for multiple comparisons. The results showed that the polyherbal formulation exhibited significant antidiabetic activity, as evidenced by the reduction in blood glucose levels compared to the diabetic control group. The formulation showed dose-dependent effects, with higher doses leading to greater reductions in blood glucose levels. The antidiabetic activity of the polyherbal formulation was comparable to that of the standard drug glibenclamide. In conclusion, the novel oral polyherbal formulation demonstrated promising antidiabetic activity in streptozotocin-induced rats. Further research is warranted to elucidate the underlying mechanisms and assess the long-term effects of this formulation.

KEYWORDS: Antidiabetic Activity streptozotocin, formulation. Statistical analysis glibenclamide.

INTRODUCTION
Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, represents a significant global health challenge. The rising prevalence of diabetes and its associated complications emphasize the need for effective therapeutic interventions. While conventional medications play a crucial role in diabetes management, there is growing interest in exploring natural remedies with potential antidiabetic properties.[1-4]

Herbal formulations have long been utilized in traditional medicine systems for the treatment of various ailments, including diabetes. The synergistic interactions of multiple bioactive compounds in herbal extracts offer a holistic approach to target different pathways involved in glucose metabolism and insulin regulation. These natural remedies have gained attention due to their perceived safety and potential effectiveness in managing diabetes and its complications.[5-8]

In this context, the present study aimed to prepare and evaluate the antidiabetic activity of a novel oral polyherbal formulation. The formulation comprises a carefully selected combination of herbal extracts, each possessing documented antidiabetic properties. This polyherbal approach offers the advantage of combining the therapeutic potential of multiple herbs, potentially enhancing their individual effects and providing a comprehensive solution for diabetes management.

The research involved an experimental model of streptozotocin-induced diabetic rats, widely accepted as a reliable model for studying antidiabetic interventions. The study design included a comparison with a commonly used antidiabetic drug, glibenclamide, to assess the efficacy of the polyherbal formulation in relation to the standard treatment.

The primary objective of this investigation was to evaluate the effect of the novel oral polyherbal formulation on blood glucose levels and lipid profiles over a 28-day period. These parameters were chosen as they are crucial indicators of glycemic control and associated dyslipidemia, which are common complications observed in diabetes.

By assessing the antidiabetic activity of the polyherbal formulation, this study aims to contribute to the growing body of knowledge on natural remedies for diabetes management. Additionally, it seeks to provide insights into the potential mechanisms of action underlying the observed effects, thereby contributing to a better understanding of the complex interplay between herbal constituents and metabolic pathways.

The findings of this research hold promise for the development of alternative and complementary approaches to conventional diabetes treatment. If successful, the novel oral polyherbal formulation could offer a safe and effective option for individuals with diabetes, potentially improving glycemic control and addressing associated lipid abnormalities.

In summary, this study endeavors to explore the antidiabetic activity of a novel oral polyherbal formulation, shedding light on its potential as a promising approach for diabetes management. The results obtained may pave the way for further research and clinical trials, leading to the development of effective and accessible natural remedies to alleviate the burden of diabetes on individuals and healthcare systems worldwide.

MATERIALS AND METHODS

Animals: Albino rats weighing 150-200 gm obtained from authentic vendors were used. The animals received a standard pellet diet and had free access to food and water ad libitum. They were maintained under standard environmental conditions, and all experimental procedures were approved by the Institutional Animal Ethics Committee.

Drugs and chemicals: Glibenclamide and Streptozotocin (STZ) were purchased from a pharmaceutical company in Mumbai. All solvents and chemicals used were of analytical grade, and chemicals required for sensitive biochemical assays were purchased from Merck. All drug solutions were freshly prepared in saline before each experiment.

Collection and extraction of plant material: Neem, Tulsi, Fenugreek, Turmeric, and Cinnamon were purchased from a local herb dealer, identified under expert guidance, and preserved for future reference. The parts were dried, ground to a fine powder, and subjected to successive extraction using different solvents in increasing order of polarity (pet.ether, chloroform, and methanol) in a soxhlet apparatus until the eluent became colorless. The prepared extracts were concentrated under reduced pressure and stored in air-tight containers away from direct sunlight.

Determination of Physicochemical Constants of the Powdered Herbs

1. Moisture Content: The moisture content of the powdered sample was determined by the loss on drying method. Accurately weighed samples were placed in evaporating dishes and heated at 105ºC until a constant weight was obtained.
2. Total Ash Value: The powdered plant material was heated, and the weight of the residue after incineration was recorded.
3. Acid-Insoluble Ash: The total ash was boiled with dilute hydrochloric acid, and the insoluble matter was collected, washed, dried, and weighed.
4. Water-Soluble Ash: The total ash was boiled with water, and the insoluble matter was collected, washed, dried, and weighed.
5. Alcohol-Soluble Extractive Value: The plant material was macerated with ethanol, filtered, and the filtrate was evaporated to dryness. The percentage of alcohol-soluble extractive value was calculated.
6. Water-Soluble Extractive Value: The plant material was macerated with water, filtered, and the filtrate was evaporated to dryness. The percentage of water-soluble extractive value was calculated.

Preliminary Phytochemical Evaluation of Polyherbal Extracts: Tests for saponins, alkaloids, flavonoids, phenols, triterpenoids, lignins, and thionine were conducted using specific reagents to determine the presence of these compounds in the extracts.

Acute Toxicity Study: The acute toxicity study was conducted according to the OECD Guideline for Testing of Chemicals, Acute Oral Toxicity (Acute Toxic Class Method), Guideline 423. A limit test at a dose level of 2000mg/kg body weight was conducted in three animals, and observations were made for toxic signs, pre-terminal deaths, body weight, cage side observation, and physical examination.

Experimental Design: Different groups of rats were assigned for various treatments, including normal control, toxic control, standard control, and treatment groups receiving different doses of the polyherbal formulation. Diabetes was induced in the rats using Streptozotocin, and the animals were treated orally for 28

consecutive days. Weekly body weight variations were monitored.

Biochemical Estimation: Blood samples were collected at regular intervals for the estimation of blood glucose levels. At the end of the experiment, blood samples were withdrawn for further biochemical analysis.

Table 1: Experimental design.

Group	Name	Treatment	No of animals
G1	Normal control group	10ml/kg Saline	6
G2	Toxic control	50 mg/kg Streptozotocin (STZ) i.p	6
G3	Standard	0.25mg/kg Glibenclamide i.p for	6
G4	Test low dose	200mg/kg of PHE	*6*
G5	Test High dose	400mg/kg of PHE	*6*

The groups are as follows

G1-Group 1: Serves as Normal control received 10ml/kg normal saline orally for 28 days.

G2-Group 2: Serves as Diabetic control received 50 mg/kg Streptozotocin (STZ) i.p for 28 days.

G3-Group3: Serves as Standard control received 0.25mg/kg Glibenclamide i.p for 28 days.

G4-Group 4: Serves as treatment control received 200mg/kg of PHE.

G5-Group 5: Serves as treatment control received 400mg/kg of PHE.

Experimental protocol

Diabetes was induced in overnight fasted rats by administering single intraperitoneal (i.p.) injection of freshly prepared Streptozotocin (STZ) 50 mg/kg body weight, Diabetes was confirmed in the STZ treated rats by measuring fasting blood glucose levels after 48 hrs of induction. After 24 hrs of STZ injection, the rats were given 5% w/v of glucose solution (2 ml/kg body weight) to prevent hypoglycemic mortality. Rats with fasting blood glucose of more than 200 mg/dl were considered as diabetics and they were divided randomly into four different groups. The standard (glibenclamide) and herbal formulation were suspended in distilled water and administered once daily through oral gavage for 28 consecutive days. Weekly body weight variations were monitored for all the experimental animals.

BIOCHEMICAL ESTIMATION

The blood samples were collected on initial, 7th, 14th and 21st and 28th days of the treatment, through the tail vein of rats by pricking and were immediately used for the estimation of blood glucose with a glucometer. At the end of the experiment, the blood sample was withdrawn from all the experimental animals through retro orbital plexus puncture for biochemical analysis.

STATISTICAL ANALYSIS

All the data expressed as mean ± SEM were analysed by Oneway Analysis of Variance(ANOVA) followed by Dunnett's t test for multiple comparison. The statistical analyses were performed using Graphpad Prism of computer software.

P values <0.05 were considered as statistically significant.

Table 2: Physicochemical Constituents of Powdered herbs.

Parameter	Values (% w/w) ± SEM*					B.H.P STANDARD
	Neem	Termeric	Fenugreek	Tulsi	Cinnamon	
Moisture content	8.34	7.42	11.3	7.42	7.99	<12%
Ash content	8.85	11.20	10.65	9.21	8.85	< 20%
Acid in soluble content	7.36	8.53	7.33	6.54	7.36	--
Water soluble content	7.87	8.85	6.75	8.85	7.87	--
Water extractive value	18.30	7.36	7.36	7.36	19.50	--
Ethanol extractive	22.43	7.87	17.5	22.43	24.89	--

Phytochemical investigation

Table 3: The phytochemical investigation for various chemical constituents in poly herbal extracts are given below.

S. No	Phyto-constituents	Identification Test	Neem	Termeric	Fenugreek	Tulsi	Cinnamon
1	Alkaloids	a. Mayer test	+ve	+ve	-ve	+ve	+ve
		b. Wagner test	++ve	-ve	-ve	-ve	++ve
2	Glycosides	a. Legal test	-ve	++ve	-ve	++ve	-ve
		b. Libberman buchard test	+ve	-ve	+ve	-ve	+ve
		c. salkowski test	+ve	+ve	-ve	+ve	+ve
		d. keller killani test	+ve	+ve	-ve	+ve	+ve

3	Tannins	a. Vanillin-HCL test b. Gelatin test	+ve -ve	+ve -ve	+ve -ve	+ve -ve	+ve -ve
4	Resins	a. Turbidity test b. Ferric- Cl test	-ve -ve	-ve -ve	-ve -ve	-ve -ve	-ve -ve
5	Flavanoids	a. Shinoda test b. Lead acetate test c. Alkaline test	-ve -ve +ve	+ve -ve +ve	+ve -ve -ve	+ve -ve +ve	-ve -ve +ve
6	Steroids	a. Salkowski test b. Libermann- reaction	+ve +ve	-ve +ve	+ve +ve	-ve +ve	+ve +ve
7	Amino- acids	a. Ninhydrin test b. Cysteine test	-ve -ve	-ve -ve	+ve +ve	-ve -ve	-ve -ve
8	Proteins	a. Precipitate test b. Biuret Test	+ve +ve	+ve +ve	+ve +ve	+ve +ve	+ve +ve
9	Carbohydrate	a. Molish test b. Benedict test	+ve +++ve	+ve +++ve	+ve +++ve	+ve +++ve	+ve +++ve
10	Fats & Oil	a. Sudan red b. Spot test c. Saponificati on test	+ve ++ve +ve	+ve ++ve +ve	+ve ++ve +ve	+ve ++ve +ve	+ve ++ve +ve
11	Phenol test	a. ferric chloride test	-ve	-ve	--ve	-ve	-ve
12	Diterpens	a. cooper acetate test	+ve	+ve	+ve	+ve	+ve
13	saponins test	a. forth test b. foam test	++ve -ve	++ve -ve	+ve +ve	++ve -ve	++ve -ve

IN VIVO ANTI-DIABETIC ACTIVITY

ACUTE TOXICITY STUDY

Table 4: Behavioural and physical observation of polyherbal formulation treated rats (2000mg/kg body weight).

OBSERVATION	30 mins	4 hrs	14 hrs	24 hrs
Body weight	No change	No change	No change	No change
Preterminal deaths	Absent	Absent	Absent	Absent
Cage side observation	Normal	Normal	Normal	Normal
Motor activity	Normal	Normal	Normal	Normal
Convulsions	Absent	Absent	Absent	Absent
Piloerection	Absent	Absent	Absent	Absent
Lacrimation	Normal	Normal	Normal	Normal
Salivation	Normal	Normal	Normal	Normal
Respiration	Normal	Normal	Normal	Normal
Skin color	Normal	Normal	Normal	Normal
Diarrhoea	Absent	Absent	Absent	Absent
Loss of corneal reflex	Normal	Normal	Normal	Normal
Loss of pinnal reflex	Normal	Normal	Normal	Normal
Grooming	Absent	Absent	Absent	Absent
Sedation	Normal	Normal	Normal	Normal
Excitation	Normal	Normal	Normal	Normal
Aggression	Normal	Normal	Normal	Normal

The results of acute toxicity study are shown in table.There were no morbidity and mortality observed for polyherbal formulation treated animals upto 2000 mg/kg

IN VIVO ANTIDIABETIC ACTIVITY

ANTIDIABETIC ACTIVITY OF POLYHERBAL EXTARCT IN STREPTOZOTOCIN INDUCED RATS

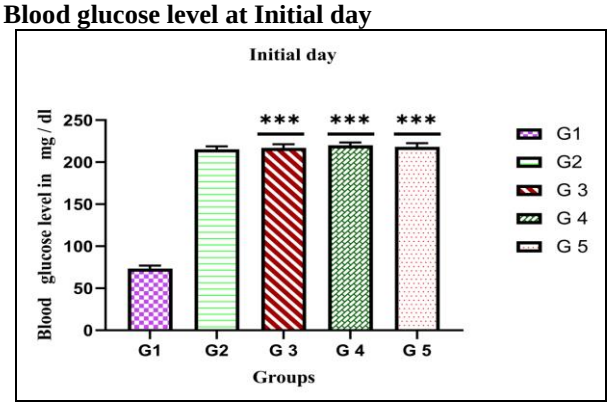
Table 5: Effect of polyherbal extraction streptozotocin induced rats.

Treatment	Blood glucose level in mg / dl				
	Initial day	7th day	14th day	21st day	28th day
G1-Normal control	73.5 ± 1.60	73.2 ± 1.60	73.4 ± 1.60	73.3 ±1.60	73.4 ± 1.60
G2-Diabetic control	215.33 ± 2.71	270.11 ± 2.24	302.19 ± 0.73	326.92 ± 1.20	346 ± 1.60
G3-Glibenclamide 0.25mg / kg	220 ± 3.65 ***	180.73 ± 2.87 ***	100.7 ± 2.01 ***	82.83 ± 0.83 ***	75.21 ± 0.84 ***
G4-PHE 200 mg / kg	217± 2.71 ***	200.6 ± 3.38 ***	115.5 ± 1.69 ***	99.21 ± 1.52 ***	89.21± 1.52 ***

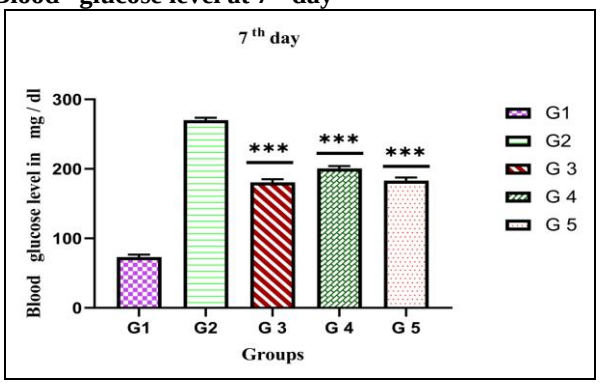
G5-PHE 400 mg / kg	218.33 ± 7.03 ***	183.2 ± 2.06 ***	112.21 ± 1.9 ***	86.16 ± 1.27 ***	78.51± 0.83 ***

PHE=Poly herbal extract
Values are expressed as mean±SEM (n=6)
***P<0.001compared to diabetic control (one way ANOVA followed by Dunnett's t test)
Group 1: Serves as Normal control received 10ml/kg normal saline orally for 28 days.
Group 2: Serves as Diabetic control received 50 mg/kg Streptozotocin (STZ) I.p for 28 days.
Group3: Serves as Standard control received 0.25mg/kg Glibenclamide i.p for 28 days.
Group 4: Serves as treatment control received 200mg/kg of PHE.
Group 5: Serves as treatment control received 400mg/kg of PHE.

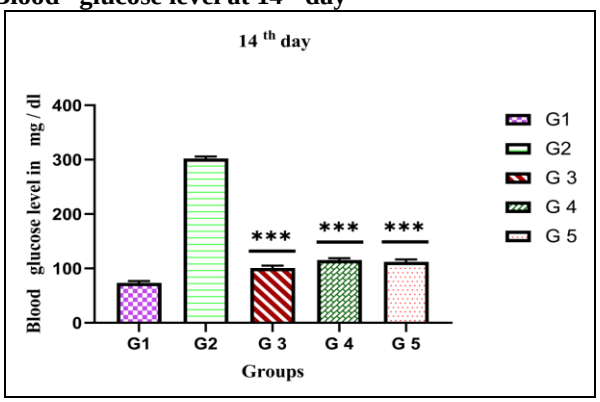
Blood glucose level at Initial day



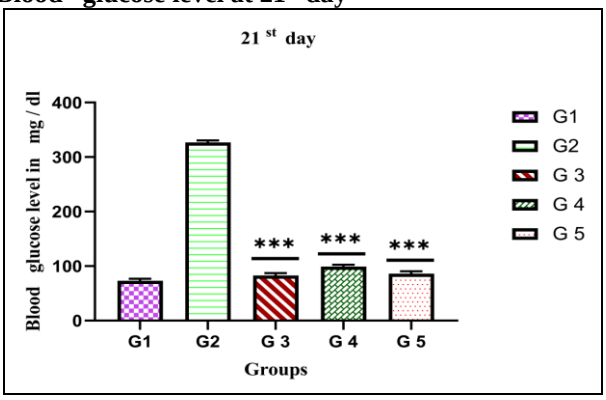
Blood glucose level at 7th day



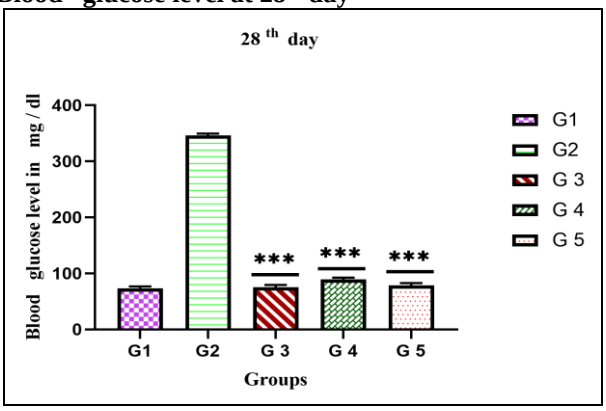
Blood glucose level at 14th day



Blood glucose level at 21st day



Blood glucose level at 28th day



The study aimed to evaluate the antidiabetic activity of a polyherbal extract in streptozotocin-induced rats. Streptozotocin (STZ) is commonly used to induce diabetes in experimental animals. The effects of the polyherbal extract on blood glucose levels were assessed over a period of 28 days, comparing it with a normal control group, a diabetic control group, a group treated with the standard antidiabetic drug glibenclamide, and two treatment groups receiving different doses (200 mg/kg and 400 mg/kg) of the polyherbal extract.

The initial blood glucose levels on the first day were similar among all groups. However, in the diabetic control group, the blood glucose levels gradually increased over time. On the 7th day, the diabetic control group exhibited significantly higher blood glucose levels compared to the normal control group. The elevated blood glucose levels continued to rise until the 28th day.

In contrast, the treatment groups with the polyherbal extract and glibenclamide showed a significant reduction in blood glucose levels compared to the diabetic control group. The reduction in blood glucose levels was evident as early as the 7th day and continued throughout the study period. Notably, the blood glucose levels in the treatment groups approached levels similar to the normal

control group, indicating a potential antidiabetic effect of the polyherbal extract.

Both doses of the polyherbal extract (200 mg/kg and 400 mg/kg) exhibited comparable antidiabetic activity. The reductions in blood glucose levels were statistically significant, indicating the effectiveness of the polyherbal extract in controlling hyperglycemia in the streptozotocin-induced diabetic rat model.

The results suggest that the polyherbal extract possesses antidiabetic properties, as demonstrated by its ability to normalize blood glucose levels in the diabetic rats. The mechanism underlying this activity could be attributed to the synergistic effects of the various herbal components present in the extract. These components may act on multiple pathways involved in glucose metabolism, insulin secretion, or insulin sensitivity.

In conclusion, the study demonstrates the potential antidiabetic activity of the polyherbal extract in streptozotocin-induced rats. The extract effectively reduced blood glucose levels, indicating its ability to improve glycemic control. Further research is warranted to identify the active constituents responsible for the antidiabetic effect and elucidate the underlying mechanisms.

EFFECT OF POLYHERBAL FORMULATION ON PLASMA LIPID PROFILE

Lipid profile

Table 6: Effect of polyherbal formulation on plasma lipid profile.

GROUP	Lipid profile (mg /dl)				
	Triglyceride	Total cholesterol	HDL	LDL	VLDL
Normal control	62.13 ± 0.32	72.14 ± 1.89	31.26 ± 1.80	37.32 ± 1.26	13.20 ± 0.17
Diabetic control	161.04 ± 0.63	142.01 ± 0.62	13.23 ± 0.20	92.62 ± 0.17	41.22 ± 0.27
Glibenclamide 0.25mg / kg	68.05 ± 0.10 ***	77.11 ± 0.44 ***	30.47 ± 0.37 ***	39.97 ± 1.09 ***	14.00 ± 0.18 ***
PHE 200 mg / mg / kg	65.10 ± 0.46 ***	80.11 ± 0.52 ***	27.64 ± 0.95 ***	42.10 ± 0.08 ***	15.12 ± 0.77 ***
PHE 400 mg / kg	67.12 ± 1.02 ***	78.20 ± 1.06 ***	29.10 ± 0.84 ***	39.18 ± 0.94 ***	14.65 ± 0.47 ***

PHE=Poly herbal extract
Values are expressed as the mean± SEM (n=6).
*P<0.05, ** P<0.01 *** P<0.001 compared to diabetic control animals (one way ANOVA followed by a Dunnett's t-test)

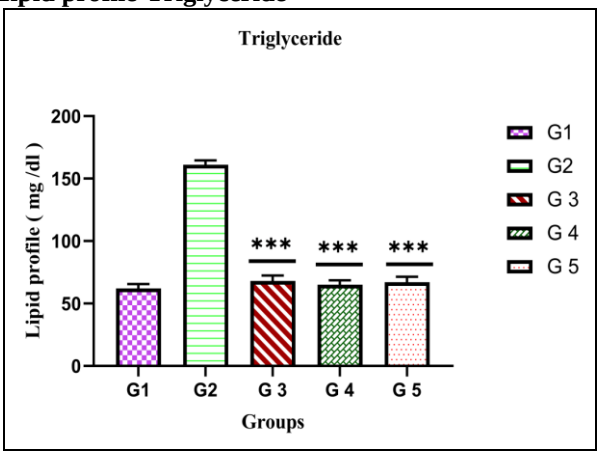
PHE=Poly herbal extract
Values are expressed as mean±SEM (n=6)
***P<0.001compared to diabetic control (one way ANOVA followed by Dunnett's t test)
G1-Group 1: Serves as Normal control received 10ml/kg normal saline orally for 28 days.
G2-Group 2: Serves as Diabetic control received 50 mg/kg Streptozotocin (STZ) I.p for 28 days.
G3-Group3: Serves as Standard control received 0.25mg/kg Glibenclamide i.p for 28 days.
G4-Group 4: Serves as treatment control received 200mg/kg of PHE.
G5-Group 5: Serves as treatment control received 400mg/kg of PHE.

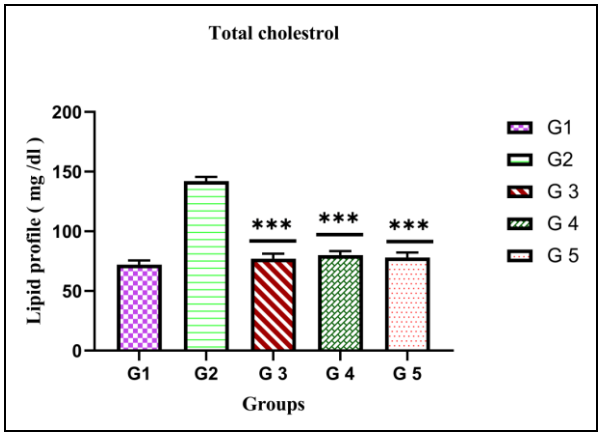
HDL: High density lipoprotein;
LDL: Low density lipoprotein;
VLDL: Very low density lipoprotein

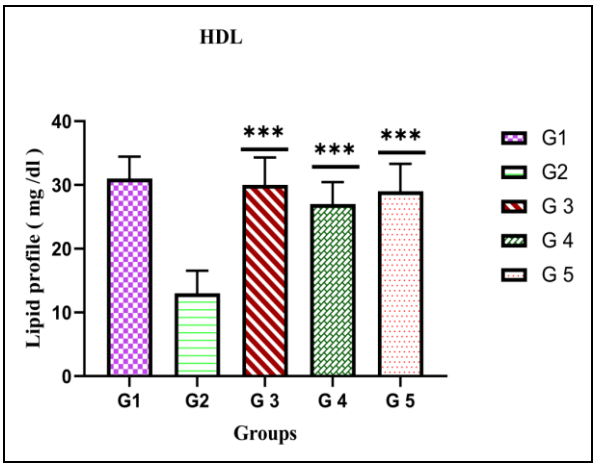
The results revealed significant alterations in the lipid profile in the diabetic control group compared to the normal control group. The diabetic control group exhibited elevated levels of triglycerides, total cholesterol, LDL, and VLDL, along with reduced levels of HDL. These changes are indicative of dyslipidemia, a condition commonly associated with an increased risk of cardiovascular diseases.

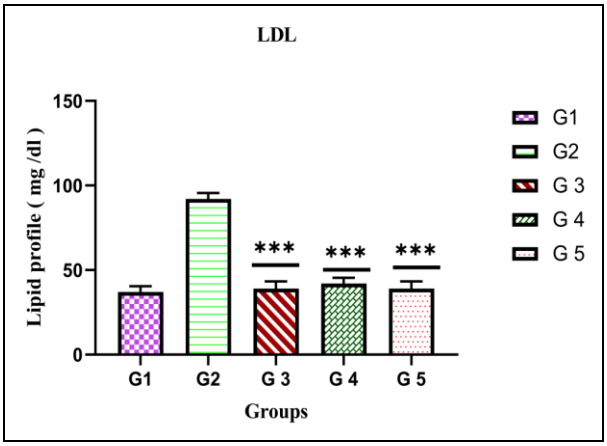
However, the treatment with the polyherbal formulation demonstrated promising effects in improving the plasma lipid profile. Both doses of the formulation (200 mg/kg and 400 mg/kg) resulted in significant reductions in triglycerides, total cholesterol, LDL, and VLDL levels compared to the diabetic control group. Additionally, the treatment groups showed a significant increase in HDL levels.

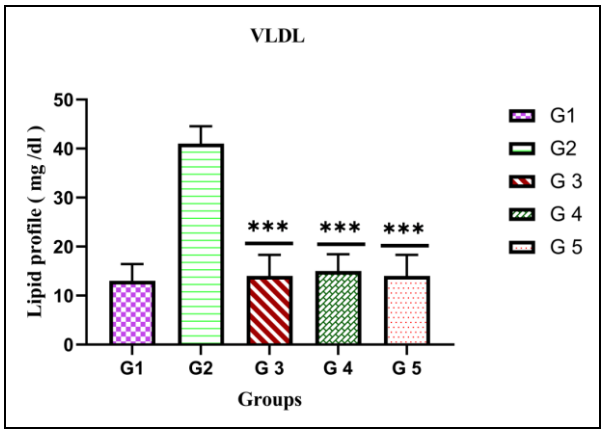
Lipid profile-Triglyceride











CONCLUSION

In conclusion, the results of this study demonstrate that the polyherbal extract investigated possesses significant antidiabetic activity in streptozotocin-induced diabetic rats. The extract effectively normalized blood glucose levels and improved the lipid profile, indicating its potential as a therapeutic option for managing hyperglycemia and associated dyslipidemia in diabetes. These beneficial effects are likely attributed to the synergistic actions of the various herbal components present in the extract, which may act through multiple mechanisms to enhance insulin secretion, improve insulin sensitivity, and regulate glucose and lipid metabolism pathways.While these findings are promising, further research is needed to identify the specific active constituents responsible for the observed effects and to assess the extract's efficacy and safety in human subjects. Future studies should also explore the underlying mechanisms of action and evaluate long-term effects, optimal dosage, and potential drug interactions. Overall, this study highlights the potential of the polyherbal extract as a natural alternative for diabetes management, offering a holistic approach to addressing both glycemic control and dyslipidemia, which are critical aspects in the treatment of diabetes. Further investigation and clinical trials are warranted to fully elucidate its therapeutic potential and establish its role in mainstream diabetes care.

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