International Journal of Chemistry and Pharmaceutical Sciences

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Research Article **Open Access**

Antidiabetic Activity of a Polyherbal Preparation in Streptozotocin-Nicotinamide (STZ-NICO) Induced Diabetic Rats

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A B S T R A C T

The present work was executed to evaluate the anti-diabetic potency of a polyherbal preparation. The objective of this study is to induce experimental diabetes mellitus using Alloxan in normal Albino wistar rats and study the antidiabetic activity of polyherbal formulation by comparison of changes in body weight and levels of glucose between normal and diabetic rats. Hypoglycemic agents from natural and synthetic sources are available for treatment of diabetes. Indian medicinal plants have been found to be useful to successfully manage diabetes. The effect of alcoholic extract of poly herbal preparation containing leaves of *Gymnema sylvestre*, fruits of *Momordica charantia*, rhizomes of *Curcuma longa*, seeds of *Eugenia jambolana* and fruits of *Embilica officinalis* was investigated in normal, glucose load conditions and alloxan induced diabetic rats. Significant anti diabetic activity was exhibited by the poly herbal formulation. Serum cholesterol levels were found to be increased in diabetic animals. Treatment with the polyherbal Preparation 200 mg/kg body wt and 400 mg/kg body wt for 10 days in diabetic animals has shown significant decrease in serum glucose and biochemical parameters (urea, creatinine, triglycerides and cholesterol) levels in comparison to control animals.

Keywords: *Gymnema sylvestre*, *Momordica charantia Curcuma longa*, *Eugenia jambolana*, *Embilica officinalis*, Polyherbal Formulation.

A R T I C L E I N F O

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Article History: Received 16 September 2015, **Accepted** 24 October 2015, **Available Online** 27 January 2016

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Manuscript ID: IJCPS2775

PAPER-QR CODE

Citation: Amit Agrawal. Antidiabetic Activity of a Polyherbal Preparation in Streptozotocin-Nicotinamide (STZ-NICO) Induced Diabetic Rats. *Int. J. Chem, Pharm, Sci.*, 2016, 4(1): 07-13.

1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterised by altered carbohydrate, lipid and protein metabolism [1]. The management of diabetes mellitus is considered a global problem and successful treatment is yet to be discovered. The modern drugs, including insulin and oral hypoglycemic agents, control the blood sugar level as long as they are regularly administered and they also produce a number of undesirable effects [2,3]. The treatment of diabetes mellitus has been attempted with different indigenous plants and polyherbal formulations [2,4,5].Traditional medicines all over the world have advocated the use of herbs to treat diabetes since time immemorial. Many Indian plants have been investigated for their beneficial use in different types of diabetes and reports occur in numerous scientific journals [6]. In the Ayurvedic system of medicine, as mentioned in ancient Indian books like Charak, Samhita, Mahdhav Nidan and Astang Sanghra, there are about 600 plants, which are stated to have antidiabetic property [7].

Wide arrays of plant derived active principles representing numerous phytochemicals have demonstrated consistent hypoglycemic activity and their possible use in the treatment of diabetes mellitus. Indian plants which are most effective and commonly studeed in relation to diabetes and its associated complications are :Allium cepa, Allium sativum, Aloevera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Ficus bengalenesis, Gymnema sylvestre, Momordica charantia, Ocimum sanctum, Pterocarpusmarsupium, Swertia chirayita, Syzigium cumini, Tinospora cordifolia, graecum and Trigonella foenum [8, 9]. Keeping the above information in view, an indigenous polyherbal preparation was developed containing the extracts of *Gymnema sylvestre*, *Momordica charantia Curcuma longa*, *Eugenia jambolana*, *Embilica officinalis*

2. Materials and Methods

Plant material

The different fresh plant parts viz., leaves of *Gymnema sylvestre*, fruits of *Momordica charantia*, rhizomes of *Curcuma longa*, seeds of *Eugenia jambolana* and fruits of *Embilica officinalis* were collected in the months Jan 2014 to March 2014 from the in and around local areas of Bhopal District of M.P. and identified & authenticated by Dr Zia Ul Hasan, Professor, Head Dept. of Botany, Safia College of science, Bhopal, M.P., dated 22/04/2014. M.P. and were deposited in Laboratory, Voucher specimen No. 470/Bot/Safia /2014 for leaves of *Gymnema sylvestre*, 469/Bot/Safia /2014 for fruits of *Embilica officinalis*, 468/Bot/Safia /2014 for fruits of *Momordica charantia*, 467/Bo/Safia /2014 for seeds of *Eugenia jambolana* and 466/Bot/Safia /2014 for rhizomes of *Curcuma longa*

Extraction

Leaves of *Gymnema sylvestre*, fruits of *Momordica charantia*, rhizomes of *Curcuma longa*, seeds of *Eugenia jambolana* and fruits of *Embilica officinalis* were coarsely powdered and extracted with ethanol in a soxhlet apparatus exhaustively. *Gymnema sylvestre*, *Momordica charantia* *Curcuma longa*, *Eugenia jambolana*, *Embilica officinalis* were mixed properly in capsule (1:1:1:1:1) & (1:1:1:1:1) in Vati to get the polyherbal formulation.

Animals

Adult Wistar rats (180 ± 10 g) of either sex were procured from D Y Patil College of Pharmacy, Pune (Maharashtra.), India. The animals were housed in large, spacious polyacrylic cages at an ambient room temperature with 12-h light/12-h dark cycle. Rats had free access to rodent pellets diet (Hindustan Lever Ltd, Bangalore, India) and water ad libitum. Experimental protocols were approved by Institutional Ethics Committee.

Acute Toxicity Studies:

Acute oral toxicity of the polyherbal formulation was carried out as per the guidelines set by the Organization for Economic Co-operation and Development (OECD), revised draft guidelines 423. The principle involves a stepwise procedure with the use of a minimum number of animals per step to obtain sufficient information on the acute toxicity of the test substance to enable its classification. Healthy Wistar rats (3animals/dose) of either sex were used for the experiment. Overnight fasted rats were orally fed with the polyherbal formulation (Capsule & Vati) in increasing dose levels of 5, 50, 300, and 2000 mg/kg body weight, respectively. The animals were observed for their behavioral (alertness, restlessness, irritability, and fearfulness), neurological (spontaneous activity, reactivity, touch response, pain response, and gait), and autonomic (defecation and urination) profiles continuously for 24 h. After a period of 24 h, the animals were observed for 14 days for mortality[10]

Selection of Doses:

For the assessment of Antidiabetic activity, two dose level were chosen in such a way that one dose was approximately one-tenth of the maximum dose during acute toxicity studies and the other high dose was twice that of one-tenth dose (200 mg/kg, 400 mg/kg body weight)

Preparation of dosing: The dose of 200 and 400 mg/kg of polyherbal preparation was prepared by suspending appropriate quantity of capsule & Vati in 1 % w/v CMC.

Oral glucose tolerance test in normal rats animals and experimental setup:

Albino rats of either sex weighing 130 – 180 g were taken. The rats were kept fasting overnight with free access to water. During experiment the animals were divided into three groups of six animals in each group. The blood sample was taken by pricking the rat's tail. Polyherbal formulation was administered with glass syringe and microsuction canula no. 18.

Grouping of animals:

Group I Kept as negative control, i.e., neither treated with Polyherbal preparation nor standard.

Group II Treated with standard oral hypoglycemic drug, i.e., Glibenclamide (0.5 mg/kg)

Group III Treated orally with polyherbal preparation (400 mg/kg)

Determination of OGTT activity:

The blood glucose concentration of animals was measured at the beginning of the study. Then the rats were orally

treated with 3 g/kg body weight glucose solution after 30 minutes of the product and drug treatment. The measurements were repeated after 30, 90 and 150 minutes after the glucose load [11,13].

Antidiabetic activity:

Diabetes was induced in overnight-fasted rats by administering single intra peritoneal (i.p.) injection of freshly prepared streptozotocin (STZ) 50 mg/kg b.w. followed by 120 mg/kg of nicotimanide (NIC) in 0.1 M citrate buffer (pH 4.5) in a volume of 0.5 ml/kg b.wt. Diabetes was confirmed in the STZ + NIC treated rats by measuring fasting blood glucose levels after 48 h of induction. After 24 h of STZ + NIC injection, the rats were given 5% w/v of glucose solution (2 ml/kg b.w.) 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 1% w/v carboxymethyl cellulose (CMC) and administered once daily through oral gavage for 21 consecutive days. The blood samples were collected on 1st, 7th, 14th, and 21st 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. Weekly body weight variations were monitored for all the experimental animals. [15]

Group I- Normal Control i.e., neither treated with polyherbal preparation nor with standard

Group II- Diabetic Control treated with streptozotocin and nicotimanide (50 mg/kg & 120 mg/kg, i.p)

Group III- Alloxan monohydrate + Glibenclamide 0.5 mg/kg,).after 3rd day of the treatment with alloxan (125 mg/kg, i.p)

Group IV- Alloxan monohydrate + PHF Capsule (200 mg/kg b.w) after 3rd day of the treatment with alloxan (125 mg/kg, i.p)

Group V Alloxan monohydrate + PHF Capsule (400mg/kg b.w) after 3rd day of the treatment with alloxan (125 mg/kg, i.p)

Group VI Alloxan monohydrate+PHF Vati (200 mg/kg b.w) after 3rd day of the treatment with alloxan (125 mg/kg, i.p)

Group VII Alloxan monohydrate + PHF Vati (400 mg/kg b.w) after 3rd day of the treatment with alloxan (125 mg/kg, i.p)

At the end of the experiment, the blood sample was withdrawn from all the experimental animals through retro-orbital plexus puncture/posterior vena cava in plain and sodium ethylene diamine tetra acetic acid (EDTA) tubes for biochemical analysis. Finally the animals were sacrificed by diethyl ether anesthesia, and liver and pancreatic tissues were excised and used for biochemical and pathological analysis. Part of the tissue sample was preserved in an ice-cold container for biochemical analysis and the remaining was stored in 10% formalin solution for histo-pathologic analysis. [16]

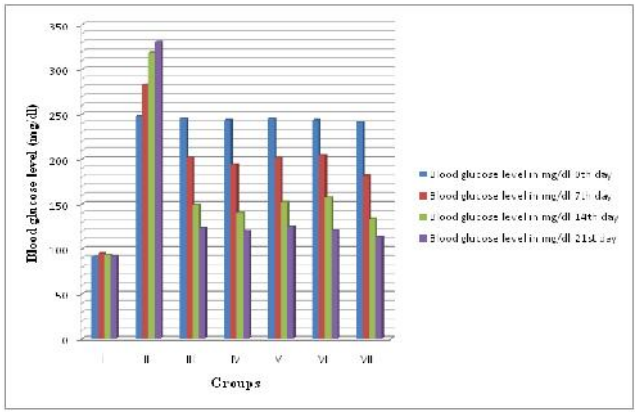
Biochemical determinations:

After the 21th day of treatment, blood was collected from the orbital plexus of overnight fasted rats. The serum was separated and urea, creatining, triglycerides, and cholesterol level were determined by using Beacon, urea determination kit, creatinine mono reagent test kit, triglycerides test kit, and cholesterol testkit (Span diagnostic Ltd, Surat), respectively. SGOT, SGPT determination kit. Serum proteins level was determined by Liquizyme, protein determination kit.

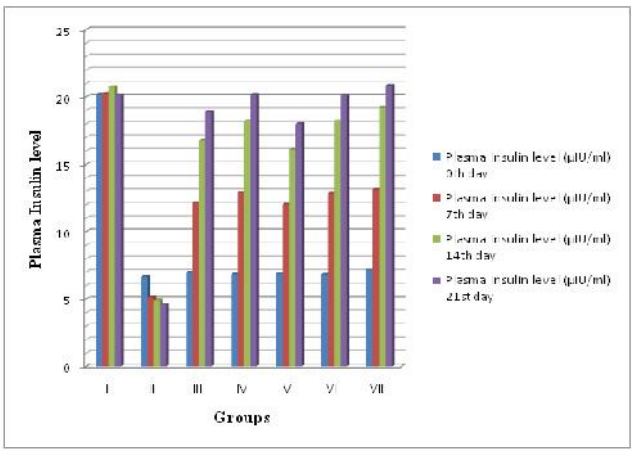
Statistical analysis: The data were expressed as mean ± SEM. The data of hypoglycemic activity, oral glucose tolerance test (OGTT), and antidiabetic activity were analysed by one-way analysis of variance (ANOVA) followed by Dunnett's ttest for multiple comparisons. Values with $P < 0.05$ were considered significant.

3. Results and Discussion

Diabetic control animals showed severe hyperglycemia compared to normal animals. The mean blood glucose level in the diabetic control group on day 0 was 247.53 ± 2.10 mg/dl and on day 21 was 330.51 ± 1.23 mg/dl. It was observed that the standard drug glibenclamide lowered the blood glucose level significantly, bringing it back to near normal level, whereas the polyherbal capsule at 200 mg/kg and 400 mg/kg significantly ($P < 0.001$) decreased the fasting blood serum glucose level in the diabetic rats on 7th, 14th, and 21st days, as compared to the diabetic control group. The results are presented in Table 1 and graph 1.

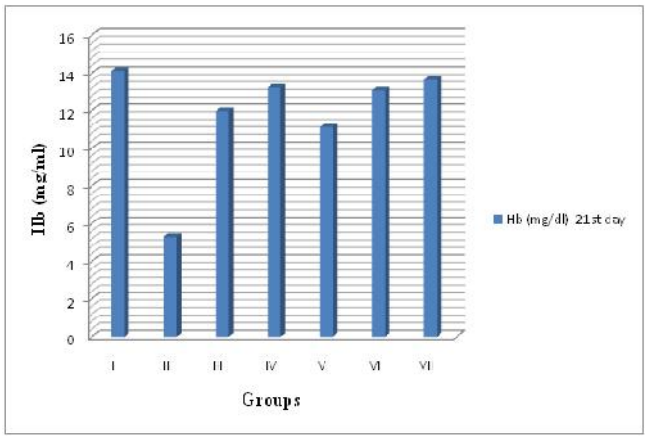


Graph 1: Graph Showing Effect of polyherbal formulation on fasting blood glucose levels (mg/dl) in STZ-and NIC-induced diabetic rats.

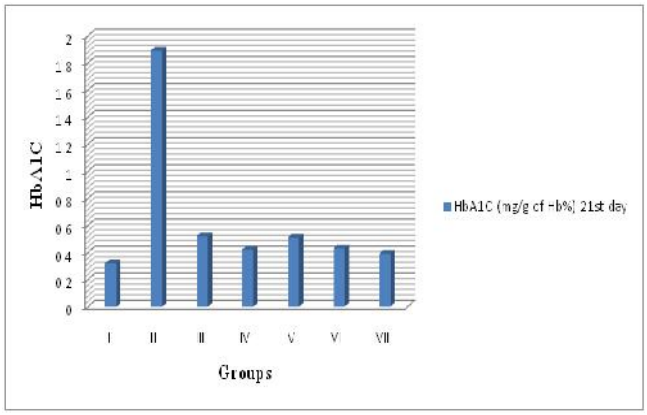


Graph 2: Graph Showing Effect of polyherbal formulation on plasma insulin level in STZ & NIC-induced diabetic rats

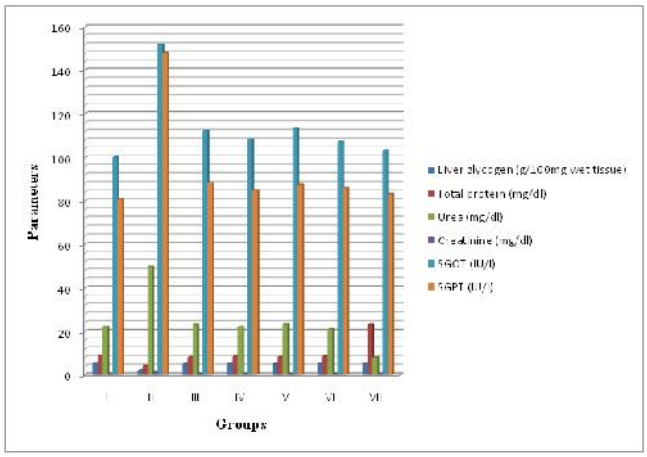
Diabetic animals showed significant decrease in plasma insulin, hemoglobin, and HbA_{1c} levels when compared with control animals. Herbal formulation and glibenclamide reversed the insulin depletion in diabetic condition and also brought back the hemoglobin and HbA_{1c} levels to normal. The results were given in table 2 and graph 3,4,5.



Graph 3: Graph Showing Effect of polyherbal formulation on Hb level in STZ-and NIC-induced diabetic rats

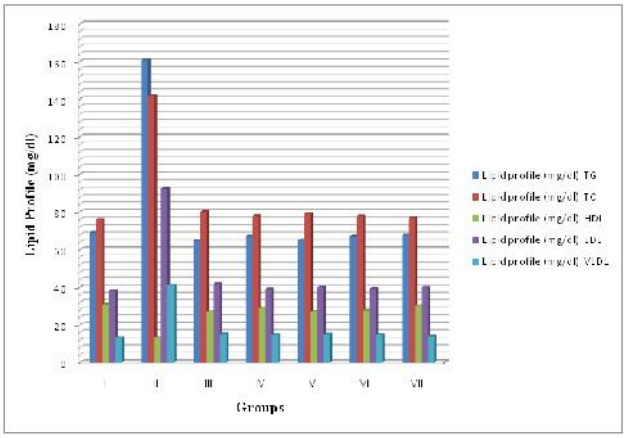


Graph 4: Graph Showing Effect of polyherbal formulation on HbA1C level in STZ-and NIC-induced diabetic rats



Graph 6: Graph Showing Effect of polyherbal formulation on serum creatinine, protein, urea, and liver glycogen levels in STZ-and NIC-induced diabetic rats

Diabetic animals showed significant reduction in liver glycogen and total protein levels when compared to the control animals, whereas herbal formulation and glibenclamide treated animals showed normal liver glycogen and total protein levels. The prevention of depletion of glycogen in the liver tissue was possibly due to stimulation of insulin release from the β cells that activates the glycogen synthase system. Effects of herbal formulation and glibenclamide on the liver and renal markers of diabetic animals are presented in table 3 and graph 6.

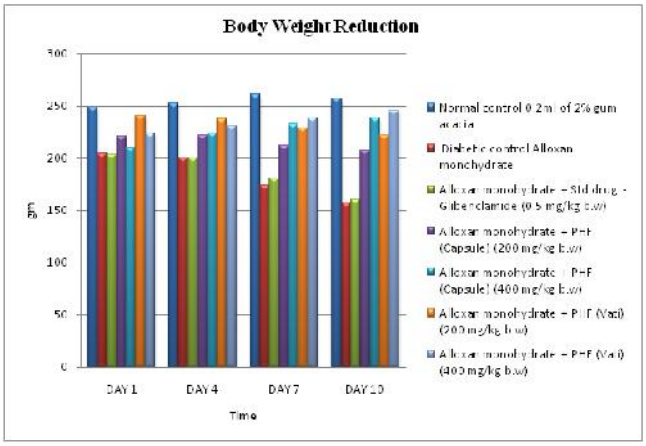


Graph 7: Graph Showing Effect of ethanolic extracts of the polyherbal formulation on serum lipids

The diabetic rats showed significant ($P < 0.001$) increase in serum lipid profiles except HDL when compared to the control animals, whereas the levels in the treatment group remained within normal limits at the end of the study. Effects of herbal formulation and glibenclamide on the lipid profile of diabetic animals are presented in table 4 and graph 7.

Average Body Weight

The rats of group I showed an average weight of while the rats of group II which received only STZ showed a very highly significant decrease in average body weight. The rats of the groups receiving Poly herbal formulation showed a dose dependent increase in average body weight. During the course of these studies average body weight were recorded on day 0, day 7, day 14 and day 21 presented in table 5 and graph 8



Graph 8: Graph Showing Effect of Poly herbal formulation (capsule & Vati) on Average Body Weight (gms) against Streptozotocin induced diabetes mellitus in rats

Solution of diazomalonaldehyde **(1)** in water was added drop wise to stirred solution of pyridine hydrochloride (1a) in water. The reaction mixture was stirred for 48 hours at room temperature. The liquid solution was concentrated. The product was obtained as yellow semisolid (scheme 4).

Table 1: Effect of polyherbal formulation on fasting blood glucose levels (mg/dl) in STZ-and NIC-induced diabetic rats

Groups	Treatments	Blood glucose level in mg/dl			
		0th day	7th day	14th day	21st day
I	Normal control 0.2ml of 2% gum acacia	91.43±0.59	95.12±1.23	93.42±1.19	92.07±1.05
II	Diabetic control STZ	247.53±2.10	282.87±2.19	318.61±1.03	330.51±1.23
III	STZ+ PHF (Capsule) (200 mg/kg)	245.03±2.01***	201.62±2.29***	148.81±1.78***	123.20±1.98***
IV	STZ + PHF (Capsule) (400 mg/kg)	243.43±2.10***	194.29±2.23***	140.51±1.90***	119.82±2.10***
V	STZ + PHF (Vati) (200 mg/kg)	245.12±2.83***	201.43±2.18***	152.20±2.65***	125.23±2.13***
VI	STZ + PHF (Vati) (400 mg/kg)	243.39±2.19***	204.31±2.43***	157.40±2.09***	120.31±1.98***
VII	STZ + Std drug - Glibenclamide (0.5 mg/kg)	241.32±2.10***	181.37±2.78***	133.43±2.15***	113.44±1.98***

PHF: Polyherbal Formulation. Values are expressed as Mean±SEM (n=6).
***p<0.001 compared to diabetic control (one-way ANOVA followed by a Dunnett's t test)
STZ: Streptozotocin, NIC: Nicotinamide

Table 2: Effect of polyherbal formulation on plasma insulin level in STZ-and NIC-induced diabetic rats

Groups	Treatments	Plasma insulin level (µIU/ml)				Hb (mg/dl)	HbA1C (Mg/g of Hb %)
		0th day	7th day	14th day	21st day	21st day	21st day
I	Normal control	20.21±0.01	20.24±0.29	20.78±0.54	20.13±0.02	14.12±0.99	0.32±0.01
II	Diabetic control	6.68±0.01	5.15±1.87	4.91±0.56	4.62±0.39	5.30±0.31	1.89±0.50
III	PHF (Capsule) (200 mg/kg)	6.98±1.48**	12.16±0.65***	16.79±0.52***	18.87±0.40***	11.96±0.41***	0.52±0.05***
IV	PHF (Capsule) (400 mg/kg)	6.82±1.20**	12.89±1.43***	18.23±1.02***	20.18±0.27***	13.23±0.58***	0.42±0.06***
V	PHF (Vati) (200 mg/kg)	6.87±1.28**	12.02±1.50***	16.12±1.08***	18.01±0.69***	11.12±0.81***	0.51±0.02***
VI	PHF (Vati) (400 mg/kg)	6.80±1.01**	12.82±1.20***	18.21±1.03***	20.12±0.89***	13.09±0.65***	0.43±0.04***
VII	Glibenclamide (0.5 mg/kg)	7.21±0.40**	13.12±0.45***	19.20±0.62***	20.87±0.10***	13.63±0.83***	0.39±0.02***

PHF: Polyherbal Formulation, Hb: Hemoglobin, HbAIC: Glycosylated hemoglobin. Values are expressed as Mean±SEM (n=6). **p<0.01, ***p<0.001 compared to diabetic control (one-way ANOVA followed by a Dunnett's t test) STZ: Streptozotocin, NIC: Nicotinamide

Table 3: Effect of polyherbal formulation on serum creatinine, protein, urea, and liver glycogen levels in STZ-and NIC-induced diabetic rats

Groups	Treatments	Liver glycogen (g/100mg wet tissue)	Total protein (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	SGOT (IU/I)	SGPT (IU/I)
I	Normal control	5.52±1.03	8.98±0.12	22.10±0.11	0.42±0.11	100.12±2.81	80.89±0.09
II	Diabetic control	2.10±0.05	4.12±10.08	49.92±0.59	1.10±0.06	151.90±1.39	148.00±2.01
III	PHF(Capsule) (200 mg/kg)	5.02±1.04***	8.20±0.07*	23.01±0.61***	0.53±0.76*	112.21±2.36***	88.21±1.21***
IV	PHF(Capsule) (400 mg/kg)	5.21±0.71***	8.44±0.71**	22.10±0.48***	0.49±0.02**	108.29±2.22***	84.81±1.91***

V	PHF (Vati) (200 mg/kg)	5.03±1.06***	8.24±0.09*	23.2±0.62***	0.52±0.64**	113.49±2.39***	87.38±1.20***
VI	PHF (Vati) (400 mg/kg)	5.29±0.88***	8.54±0.81**	21.02±0.51***	0.48±0.05**	107.23±2.36***	85.71±1.90***
VII	Glibenclamide (0.5 mg/kg)	5.41±0.52***	23.01±0.57***	8.12±0.68**	0.40±0.08**	103.21±2.14***	83.24±1.41***

PHF: Polyherbal Formulation. Values are expressed as Mean±SEM (n=6). ** p<0.01, ** p<0.01, ***p<0.001 compared to diabetic control (one-way ANOVA followed by a Dunnett's t test) STZ: Streptozotocin, NIC: Nicotinamide

Table 4: Effect of ethanolic extracts of the polyherbal formulation on serum lipids

Groups	Treatments	Lipid profile (mg/dl)				
		TG	TC	HDL	LDL	VLDL
I	Normal control	69.10±0/28	76.10±1.89	31.01±0.92	38.09±1.56	13.18±0.62
II	Diabetic control	160.87±0.61	141.90±0.59	13.18±0.18	92.59±0.21	41.16±0.25
III	PHF (Capsule) (200 mg/kg)	64.89±0.48***	80.10±0.49***	27.12±0.98***	41.90±0.07***	15.16±0.87***
IV	PHF (Capsule) (400 mg/kg)	67.12±1.03***	78.16±1.03***	28.91±0.82***	39.10±0.92***	14.82±0.45***
V	PHF (Vati) (200 mg/kg)	65.12±0.44***	79.16±0.50***	27.22±0.96***	40.12±0.06***	15.05±0.86***
VI	PHF (Vati) (400 mg/kg)	67.23±1.09***	78.01±1.01***	27.88±0.80***	39.14±0.90***	14.81±0.44***
VII	Glibenclamide (0.5 mg/kg)	68.01±0.09***	77.09±0.46***	30.21±0.36***	39.97±1.05***	14.00±0.16***

PHF: Polyherbal Formulation. Values are expressed as Mean±SEM (n=6). ** p<0.01, ** p<0.01, ***p<0.001 compared to Triglycerides, TC: Total Cholesterol, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

Table 5: Effect of Poly herbal formulation (capsule & Vati) on Average Body Weight (gms) against Streptozotocin induced diabetes mellitus in rats

Groups	Treatments	Average Body weight (in gms)			
		1th day	7th day	14th day	21st day
I	Normal control 0.2ml of 2% gum acacia	248.48±8.11	251.90±9.83	261.12±10.37(NS)	257.23±11.09(NS)
II	Diabetic control STZ	203.83±7.54	200.16±6.51	173.56±6.67**	156.8±7.61**
III	STZ+ PHF (Capsule) (200 mg/kg)	220.82±9.49	222.17±10.75	212.30±10.82*	207.18±11.12**
IV	STZ + PHF (Capsule) (400 mg/kg)	210.17±12.18	223.98±12.03	232.20±11.14*	238.78±10.12**
V	STZ + PHF (Vati) (200 mg/kg)	240.13±9.15	237.13±9.17	228.80±12.58*	222.12±13.83**
VI	STZ + PHF (Vati) (400 mg/kg)	223.87±6.71	230.42±5.76	238.80±4.76*	245.50±4.27**
VII	STZ + Std drug-Glibenclamide (0.5 mg/kg)	203.17±4.91	200.67±4.94	180.92±7.63*	160.00±8.69**

n = 6 (Number of animals in each group) DAY 1 compared with DAY 21

*p< 0.05 significant; **p<0.01 highly significant; ***p< 0.001 very highly significant; p> 0.05 non-significant (NS)

4. Conclusion

Thus, our study findings demonstrate the antidiabetic effect of the polyherbal formulation at the dose levels of 200 and 400 mg/kg. The antidiabetic potential of the polyherbal formulation is comparable with that of glibenclamide, which is evidenced by decreased levels of blood glucose, HbA1c, total cholesterol, triglyceride, low density lipoprotein (LDL)-cholesterol, urea, creatinine, SGOT, and SGPT and increase in plasma insulin, HDL-cholesterol, liver glycogen, and total protein levels.

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