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Research Article

POLYHERBAL PREPARATION AND COMPARATIVE STUDIES ON DIET-INDUCED HYPERLIPIDEMIA

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ABSTRACT

Objective: The objective of this research article is to develop and evaluate polyherbal preparation and comparative studies on diet-induced hyperlipidemia.

Methods: After the extraction, pharmacognostical and phytochemical screening was done. The lipid-lowering activity of polyherbal formulation (T1, T2, T3, T4, and T5) may be attributed to the phytoconstituents present such as alkaloids, carbohydrates, steroids, proteins, tannins, carbohydrates, flavonoids, phenols, glycosides, and triterpenes. In acute oral toxicity study, there were no behavioral changes seen up to 4 h and no mortality was observed up to the end of 24 h even at the maximum tested dose level of 2000 mg/kg per oral. It was considered maximum safe dose. Male and female albino rats weighing 150–200 g were used for the study. Hydroalcoholic extract of all plants was prepared having a dose of 2000 mg/kg. The doses were selected according to the Organisation for Economic Cooperation and Development guideline no. 425. The procedure was divided into two phases: Phase I (observation made on day 1) and Phase II (observed the animals for the next 14 days of drug administration). Animals received a single dose of 2000 mg/kg. After the administration of Healthcare Administration, food was withheld for 3–4 h. In case animal dies, we have to again perform the test for the determination of LD_{50}. The study was conducted by measuring various parameters, namely, daily feed intake (g), water intake (ml), body weight (g), lipid profile high-density lipoprotein (HDL), low-density lipoprotein (LDL), Cholesterol (CHL) level (mg/dl), and blood glucose level (mg/dl).

Results: Results showed a significant decrease in blood glucose level and serum lipid profile such as total cholesterol, LDL, and increasing serum HDL level, so could be useful in the treatment of hypolipidemia.

Conclusion: Polyherbal formulations (T1, T2, T3, T4, and T5) have hypoglycemic activity and significantly improve lipid profile levels in diet-induced experimental rats.

Keywords: Hyperlipidemia, Atherosclerosis, *Allium sativum, Moringa oleifera, Cicer arietinum, Hibiscus rosa-sinensis, Quisqualis indica.*

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INTRODUCTION

Hyperlipidemia is known as a condition of an increased level of serum total cholesterol (TC), low-density lipoprotein (LDL), very LDL (VLDL), and reduced high-density lipoprotein (HDL) [1].

Cardiovascular diseases (CVDs) are a major risk factor caused by hyperlipidemia. Hyperlipidemia disease has afflicted humankind since antiquity. Hyperlipidemia, or hyperlipoproteinemia, is defined as abnormally elevated levels of one or more of triglycerides, cholesterol, cholesterol esters, and phospholipids and plasma lipoproteins including VLDL and LDL, and reduced HDL levels. These lipoproteins are deposit in the interstitial space of arteries arising from aorta, restricting the blood supply to the heart. This phenomenon is known as atherosclerosis. Due to the privilege deposition of lipoproteins, blood supply to the heart gets blocked, and thus, myocardial infarction occurs, which is usually well known as heart attack.

Among ischemic heart disease and the high mortality rate, there is a strong relation. In addition, high plasma cholesterol levels cause more than 4 million deaths in a year. Secondary hyperlipidemia often mimics familial forms of hyperlipidemia and can have similar effects. Due to secondary hyperlipidemia, risk of premature atherosclerosis increased or, when happen with severe hypertriglyceridemia, may cause pancreatitis and other consequences of the chylomicronemia syndrome [2,3].

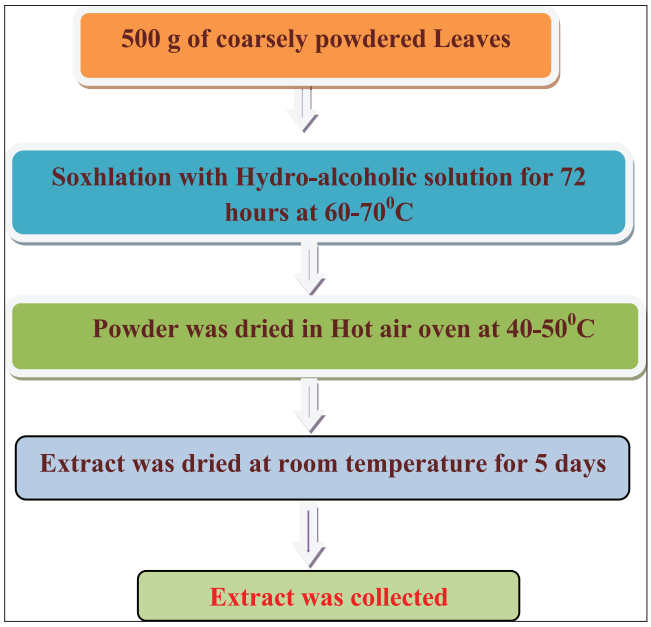


Fig. 1: Soxhlet extraction of plant parts [17,18]

From times of yore, several studies have shown that dietary modifications such as high-fiber diets, low-fat diets, and diets rich in flavonoids and phenolic acids can reduce metabolic syndrome risk factors. Statins and synthetic antioxidants such as probucol are modern antihyperlipidemic drugs which are widely used to treat atherosclerosis. Regrettably, these drugs are not free of side effects. To provide novel treatments for hyperlipidemia, it has been focused on the natural products that have very few side effects [4-6].

Table 1: Animals were grouped as follows

Group I	Normal control group (normal diet [ND])
Group II	Positive control group (ND+HFHSD)
Group III	Standard control group (HFHSD+ND+atorvastatin calcium [2.1 mg/kg, p.o. body weight])
Group IV	Test control group (HFHSD+ND+polyherbal formulation [300 mg/kg, p.o. body weight])

HFHSD: High-fat high-sugar diet

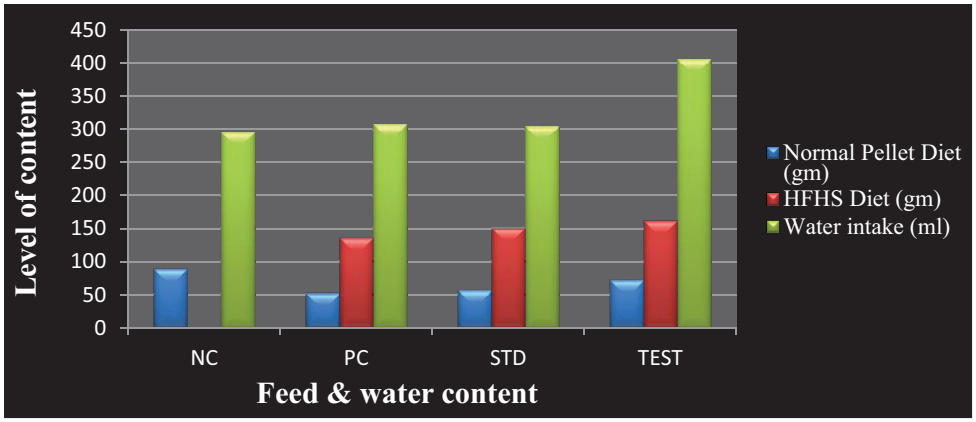
Herbs have a defined kind of potency through which they can stimulate the human body to protect itself against the diseases. These medicinal herbs serve as a great source of remedies in the treatment of human and animal diseases [7].

Here, we are in progress to prepare a polyherbal formulation which consists of the extract of *Allium sativum, Moringa oleifera, Cicer*

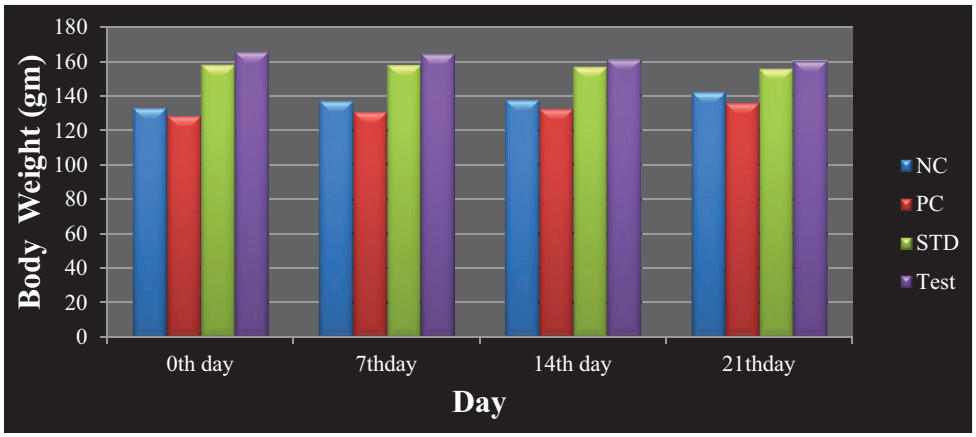
Table 2: Morphological characteristics of plants part

S. No.	Character	Observation				
		T1	T2	T3	T4	T5
1.	Color	Green	Green	Green	Deep green	Green
2.	Odor	Rough	Smooth	Rough	Slender	Waxy
3.	Taste	Pungent	Better to ingest	Sweet	Edible tangy citrusy	Simple
4.	Size	5–150 cm	2–5 cm	0.5–3 cm	6.0″ length	5–10 cm

T1: *Allium sativum*, T2: *Moringa oleifera*, T3: *Cicer arietinum*, T4: *Hibiscus rosa-sinensis*, T5: *Quisqualis indica*



Graph 1: Effect of high-fat high-sugar diet on total feed and water content. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group, following repeated measures ANOVA parametric methods, using Dunnett's test



Graph 2: Effect of high-fat high-sugar diet, atorvastatin, and *Cordia dichotoma* on body weight. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. Following repeated measures ANOVA parametric methods, using Dunnett's test. NC: Normal control group, PC: Positive control group or high-fat high-sugar diet group, standard: ND+high-fat high sugar (HFHS)+atorvastatin (2.1 mg/kg/day), test control: ND+HFHS+polyherbal formulation (300 mg/kg/day)

arietinum, Hibiscus rosa-sinensis, and *Quisqualis indica* for the treatment of hyperlipidemia.

Garlic (*A. sativum* L., family: Alliaceae) has played significant medicinal and dietary roles throughout the ages. *A. sativum* (Garlic) preparations are commercially available in the form of garlic oil and garlic powder, and pills are widely used for certain therapeutic purposes, including improving lipid profile and lowering blood pressure. Extract of *A. sativum* is alleged to possess valuable effects for the prevention of CVDs. Garlic contains active hypocholesterolemic and hypoglycemic components, known as diallyl disulfide and dipropyl disulfide; it was proven by several studies [8-10].

Leaves of *M. oleifera* Lam., Moringaceae, are claimed to possess several pharmacological activities such as cholesterol-reducing effect and are used to treat patients with heart disease and antiobesity potential that protects the body against adverse effects of high-fat diet-induced obesity. The presence of β-sitosterol in crude extracts of *M. oleifera* possesses potential hypolipidemic properties [11,12].

C. arientum reported a rich source of vitamins, minerals, and phytoestrogens. Seeds of *C. arientum* were used as stimulant, aphrodisiac, tonic, anthelminthic, appetizer, relieving burning sensation in stomach, and in the treatment of obesity and in patients who consume excess oily and heavy foods. Cholesterol-lowering effects of *C. arientum* in different types of hyperlipidemias such as induced by diet are demonstrated in several research studies [13].

H. rosa-sinensis Linn. flowers exhibited a significant reduction in serum lipid parameters such as triglycerides, TC, LDL, VLDL, and increase in HDL [14].

Cholesterol diet and passive smoking raise the lipid and cholesterol levels with reducing the HDL level which causes hypercholesterolemia and hyperlipidemia existing heart disease such as heart attack and heart stroke in the future. *Q. indica* Linn. raised the HDL level which is good cholesterol and produced a significant reduction in harmful lipids. *Q. indica* extracts contain flavonoids and phenolic compounds helpful in CVD [15,16].

Table 3: Consistency and color of all plant extracts

Extract	Solvent uses	Color	Consistency
T1	Hydroalcoholic	Dark green	Semi-solid
T2	Hydroalcoholic	Black	Semi-solid
T3	Hydroalcoholic	Black	Semi-solid
T4	Hydroalcoholic	Dark green	Semi-solid
T5	Hydroalcoholic	Dark green	Semi-solid

T1: *Allium sativum*, T2: *Moringa oleifera*, T3: *Cicer arietinum*, T4: *Hibiscus rosa-sinensis*, T5: *Quisqualis indica*

Table 4: Percentage yield of all plant extracts

S. No.	Extracts	Yield (g)	Percentage yield (%)
1.	T1	12.801	14.94
2.	T2	11.502	12.50
3.	T3	13.200	15.20
4.	T4	15.020	16.25
5.	T5	14.250	13.65

T1: *Allium sativum*, T2: *Moringa oleifera*, T3: *Cicer arietinum*, T4: *Hibiscus rosa-sinensis*, T5: *Quisqualis indica*

Table 5: Physiochemical analysis of powder of all plant leaves

S. No.	Parameters	Observation (%)				
		T1	T2	T3	T4	T5
1.	Loss on drying	1.58	2.05	1.35	1.55	1.75
2.	Total ash value	4.50	3.80	3.59	4.89	3.74
3.	Acid-insoluble ash value	0.85	1.05	0.95	1.00	1.10
4.	Water-soluble ash value	0.89	0.93	0.085	0.97	1.0
5.	Foaming index (cm)	1.00	1.25	0.62	0.5	0.45

T1: *Allium sativum,* T2: *Moringa oleifera,* T3: *Cicer arietinum,* T4: *Hibiscus rosa-sinensis,* T5: *Quisqualis indica*

METHODS

Collection of plant

A. sativum, *M. oleifera*, *C. arietinum*, *Q. indica*, *H. rosa*-sinensis, and Q. indica were collected from various places from BHEL area, Govindpura, Bhopal, Madhya Pradesh, during the month of May 2018.

Authentication of plant material

The plant has been identified and authenticated by Janata PG College, A.P.S. University, Rewa, Madhya Pradesh, voucher specimen no. is Number/J/BOT/H-332 to H-336.

Preparation of extract

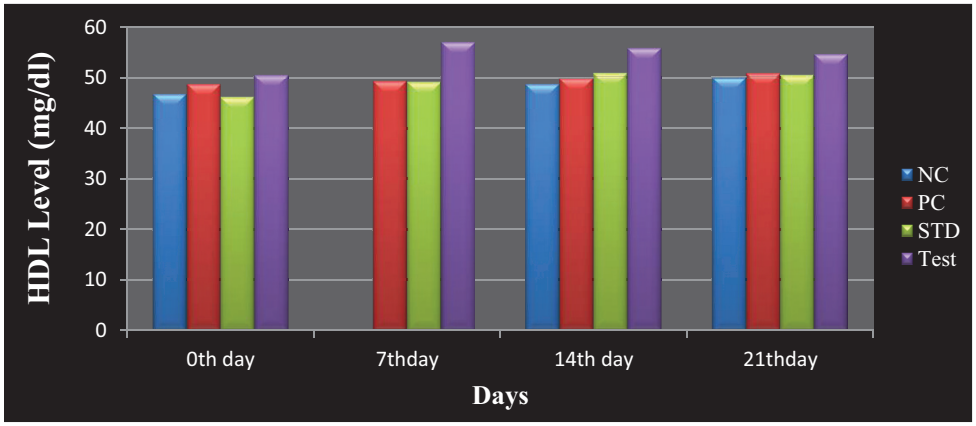
Extraction of *A. sativum*, *M. oleifera*, *C. arietinum*, *Q. indica*, H. rosa-sinensis, and Q. indica was done by Soxhlet extraction method (Fig. 1).

- Soxhlet extraction: Soxhlet apparatus was used for the extraction and hydroalcoholic solvent (1:1) was selected as a solvent for extraction and calculated percentage yield of the extract.

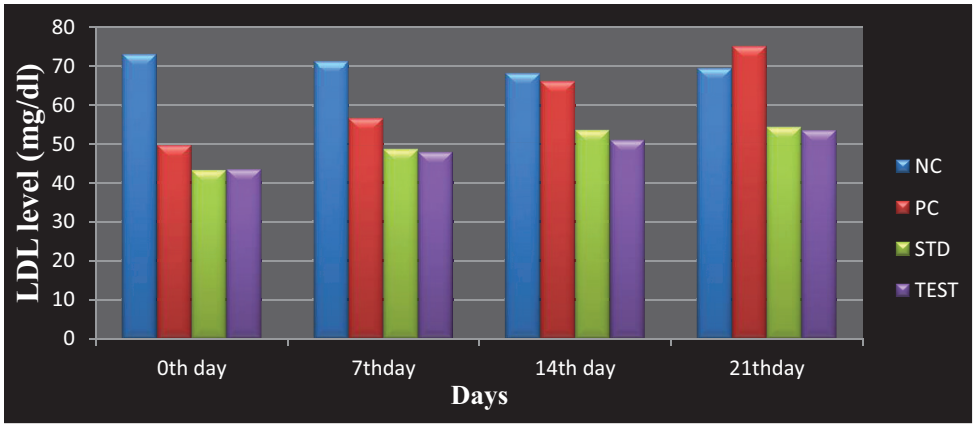
Table 6: Phytochemical screening of hydroalcoholic extract

S. No.	Identification test	Test name	T1	T2	T3	T4	T5
1.	Alkaloids	Mayer's test	+	+	−	+	+
		Dragendorff's test	+	−	+	+	−
		Wagner's test	+	+	−	+	+
2.	Glycosides	Killer-Killani test	+	+	+	−	+
3.	Carbohydrates	Molisch's test	−	−	+	+	+
		Fehling test	+	−	+	−	−
4.	Tannins and phenols	Gelatin test	+	+	+	+	+
		Ferric chloride test	+	−	+	−	+
5.	Flavonoids	Shinoda test	+	+	+	+	+
		Alkaline reagent test	−	+	+	+	+
6	Steroids	Liebermann–Burchard test	−	−	+	−	+
		Salkowski test	−	−	−	+	+
7.	Saponins	Foam test	+	+	−	−	−
8.	Protein	Xanthoproteic	+	−	+	+	+
9.	Gums and mucilage	With 95% alcohol	−	+	−	−	−

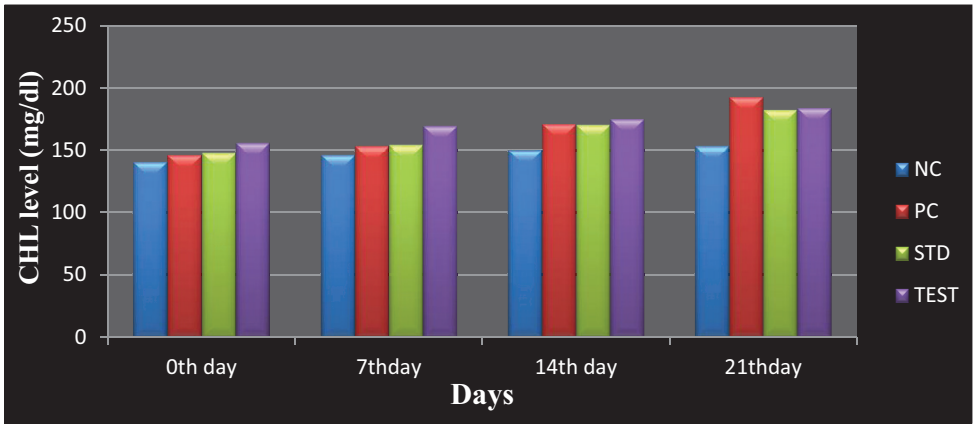
T1: *Allium sativum,* T2: *Moringa oleifera,* T3: *Cicer arietinum,* T4: *Hibiscus rosa-sinensis,* T5: *Quisqualis indica.* +: Present, −: Absent



Graph 3: Effect of high-fat high-sugar diet, atorvastatin, and *Cordia dichotoma* on HDL level. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. Following repeated measures ANOVA parametric methods, using Dunnett's test. NC: Normal control group, PC: Positive control group or high-fat high-sugar diet group, standard: ND+high-fat high sugar (HFHS)+atorvastatin (2.1 mg/kg/day), test control: ND+HFHS+polyherbal formulation (300 mg/kg/day)



Graph 4: Effect of high-fat high-sugar diet, atorvastatin, and *Cordia dichotoma* on LDL level. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. Following repeated measures ANOVA parametric methods, using Dunnett's test. NC: Normal control group, PC: Positive control group or high-fat high-sugar diet group, standard: ND+high-fat high sugar (HFHS)+atorvastatin (2.1 mg/kg/day), test control: ND+HFHS+polyherbal formulation (300 mg/kg/day)



Graph 5: Effect of high-fat high-sugar diet, atorvastatin, and *Cordia dichotoma* on CHL level. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. Following repeated measures ANOVA parametric methods, using Dunnett's test. NC: Normal control group, PC: Positive control group or high-fat high-sugar diet group, standard: ND+high-fat high sugar (HFHS)+atorvastatin (2.1 mg/kg/day), test control: ND+HFHS+polyherbal formulation (300 mg/kg/day)

Table 7: Results of acute oral toxicity study of HACD

Group name	Animal mark	Dose mg/kg	Body weight (g)			Observation	Mortality (if any)
			1 day	7 days	14 days		
Control	H	Normal saline (0.91%)	153	148	146	No sign of toxicity and all animals survived	No mortality occurs
	B		155	150	152		
	T		138	135	132		
Test	HT	2000 mg/kg polyherbal formulation	205	208	202		
	BT	(once dosing at start of acute oral toxicity study)	190	185	180		
	NM		175	165	168		

Table 8: Total feed (g) and water (ml) intake

Group	Normal pellet diet (g)	HFHSD (g)	Water intake (ml)
NC	89.38±27.53	0	296.67±66.60
PC	53.09±4.70*	135.73±18.41	307.67±86.98**
STD	57. 08±21.13*	151.16±9.99	305.00±51.57
Test	72.40±12.78	162.28±10.82	406.33±20.88

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. (Following repeated measures ANOVA (parametric methods, using Dunnett's test). HFHSD: High-fat high-sugar diet (Graph 1)

Table 9: Body weight (g)

Group	0th day	7th day	14th day	21th day
NC	133.17±3.25	137.5±3.20	138.00±1.78	142.66±1.36**
PC	128.5±2.42	130.8±2.63	133.00±2.36	136.33±1.67
STD	158.5±2.88	158.00±3.34	157.33±3.07	156.16±2.49
Test	166.00±5.03*	164.83±4.53*	161.83±4.07*	160.83±4.35

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. (Following repeated measures ANOVA (parametric methods, using Dunnett's test) (Graph 2)

Preparation of polyherbal formulation

The hydroalcoholic extract of *A. sativum* (50 mg), *M. oleifera* (50 mg), *C. arietinum* (50 mg), *H. rosa-sinensis* (50 mg), and *Q. indica* (50 mg) was dissolved in suspending agent (1% carboxymethylcellulose [CMC] aqueous) before orally administered to the rats. Standard drug was dissolved in suspending agent (1% CMC) before orally administered to the rats [19].

Preparation of high-fat high-sugar diet (HFHSD)

Bread (30 g)+Biscuits (30 g)+Vanaspati ghee (3 ml)+Coconut oil (1 ml) 25% fructose was added in drinking water bottle.

These diets were fed along with normal diet for a total period of 6 weeks to rats.

Experimental protocols

In the HFHSD model, the animals were divided into five groups and each group composed of six animals (Table 1).

All the treatments were carried out for 42 days. Before and after the treatment, the animals were fasted for 2 h to improve the absorption rate. Parameters studied for this test were body weights, blood glucose, and total high-density lipoprotein cholesterol levels.

RESULTS

- Morphology (Table 2)
- Consistency and color (Table 3)
- Practical and percentage yield (Table 4)
- Screening of powder (Table 5)
- Phytochemical screening: There is the presence of different phytochemicals in hydroalcoholic extract T1, T2, T3, T4, and T5 (Table 6).

Table 10: HDL level (mg/dl)

Group	0th day	7th day	14th day	21th day
NC	46.67±1.64	48.17±1.17	48.66±2.25	50.00±1.90
PC	48.67±2.74	49.34±2.34	49.83±1.84	50.83±1.48
STD	46.16±2.48*	49.16±2.13	50.83±2.48**	50.5±1.51
Test	50.5±2.48	57.00±3.35	55.83±3.12	54.55±2.58

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. (Following repeated measures ANOVA (parametric methods, using Dunnett's test). HDL: High-density lipoprotein (Graph 3)

Table 11: LDL level (mg/dl)

Group	0th day	7th day	14th day	21th day
NC	73.00±2.28	71.16±1.72	68.16±2.04	69.5±1.76*
PC	49.5±3.08	56.66±2.94	66.16±2.92	75.16±3.48
STD	43.16±2.31	48.67±2.58	53.5±1.76**	54.34±2.59*
Test	43.33±1.87	47.83±2.14	51.00±3.03**	53.34±2.43**

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. (Following repeated measures ANOVA (parametric methods, using Dunnett's test). LDL: Low-density lipoprotein (Graph 4)

Table 12: CHL level (mg/dl)

Group	0th day	7th day	14th day	21th day
NC	140.34±3.67	146.17±3.31	150.34±3.45	153.5±2.95**
PC	146.00±1.42	153.5±2.58	170.66±4.58	192.5±2.74
STD	148.00±3.46	154.33±1.86*	170.34±3.07	182.00±4.60
Test	156.00±2.36	169.66±3.15	174.67±2.43	183.5±2.50

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. (Following repeated measures ANOVA (parametric methods, using Dunnett's test) (Graph 5)

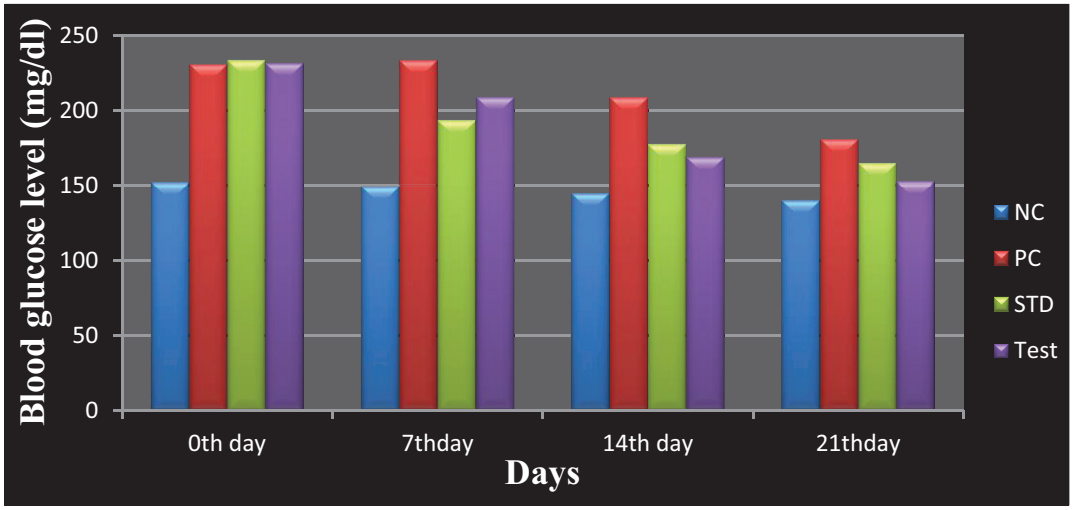
- Antihyperlipidemic activity of polyherbal formulation from diet-induced model on experimental rats Acute toxicity studies (LD_{50}): In both Phase I and Phase II procedures, none of the animal mortal or any signs of behavioral changes or show any toxicity on the single administration of Healthcare Administration (2000 mg/kg p.o.). Thus, 300 mg/kg dose was selected for the present study (Table 7).

Evaluation parameters

- Effect on feed (g) and water (ml) intake (Table 8)
- Effect on body weight (g) (Table 9)
- Effect on HDL level (mg/dl) (Table 10)
- Effect on LDL level (mg/dl) (Table 11)
- Effect on CHL level (mg/dl) (Table 12)
- Effect on blood glucose level (mg/dl) (Table 13)

Graphical representation

- Effect on total feed and water intake
- Effect on body weight
- Effect on HDL level



Graph 6: Effect of high-fat high-sugar diet, atorvastatin, and *Cordia dichotoma* on blood glucose level. Values are expressed as mean±standard deviation; (n=6). All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group. Following repeated measures ANOVA parametric methods, using Dunnett's test. NC: Normal control group, PC: Positive control group or high-fat high-sugar diet group, standard: ND+high-fat high sugar (HFHS)+atorvastatin (2.1 mg/kg/day), test control: ND+HFHS polyherbal formulation (300 mg/kg/day)

Table 13: Blood glucose level (mg/dl)

Group	0th day	7th day	14th day	21th day
NC	152.5±1.87**	149.5±1.87**	144.84±2.13**	140.67±3.01*
PC	230.83±2.31	234.00±2.60	209.34±5.16	180.84±10.18
STD	233.84±4.84	193.67±6.98*	177.83±3.43	165.16±5.11
Test	232.00±5.97	209.34±6.12	169.33±7.97	152.8±4.13

All values are mean±standard error of mean, n=6. *p<0.05, **p<0.01 when compared to positive control group.
(Following repeated measures ANOVA (parametric methods, using Dunnett's test)

- Effect on LDL level
- Effect on CHL level
- Effect on blood glucose level

DISCUSSION

The study was carried out to evaluate antihyperlipidemic activity of polyherbal formulation (T1, T2, T3, T4, and T5) in HFHSD-induced model of rats.

The coarse powder of the shed dried part of the plant was subjected to extraction using Soxhlet apparatus. The plant material was extracted with hydroalcoholic solvent system (1:1). The obtained practical yield of extract sequentially (T1, T2, T3, T4, T5) was 12.801 g, 11.502 g, 13.200gm, 15.020 g, and 14.250 g or percentage yield of extract was 14.94%, 12.50%, 15.20%, 16.25%, and 13.65%.

After the extraction, pharmacognostical and phytochemical screening was done. The lipid-lowering activity of polyherbal formulation (T1, T2, T3, T4, and T5) may be attributed to the phytoconstituents present such as alkaloids, carbohydrates, steroids, proteins, tannins, carbohydrates, flavonoids, phenols, glycosides, and triterpenes.

In acute oral toxicity study, there were no behavioral changes seen up to 4 h and no mortality was observed up to the end of 24 h even at the maximum tested dose level of 2000 mg/kg per oral. It was considered maximum safe dose.

The study was conducted by measuring various parameters, namely, daily feed intake (g), water intake (ml), body weight (g), lipid profile HDL, LDL, CHL level (mg/dl), and blood glucose level (mg/dl).

CONCLUSION

We can say that polyherbal formulations (T1, T2, T3, T4, and T5) have hypoglycemic activity and significantly improve lipid profile levels in diet-induced experimental rats. Results showed significant decrease in blood glucose level and serum lipid profile such as TC, LDL, and increasing serum HDL level, so could be useful in the treatment of hypolipidemia as mentioned in traditional medicine. However, further studies required to isolate the phytochemicals those responsible for hypolipidemic activity.

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AUTHORS' CONTRIBUTIONS

All the authors have equally contributed.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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