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Anti-Hyperlipidemic Activity of Ursolic Acid Derivative Obtained from Lantana Camara

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Abstract *Lantana camara* is to be a tackler in Indian ethanopharmacology. It is found commonly every where even on waste land, road side, dry places and spread vigorously on cultivated ground. The aim of present study is to evaluate pharmacological effect ursolic acid steroyl glucoside obtained from *lantana* camara on lipid profile of high fat diet (58%) induced hyperlipidemia. Administration of high fat diet increase the lipid profile of the animals significantly as compared to normal control. Treatment with the ursolic acid steroyl glucoside for 12 weeks. Decreased the lipid parameters as compared to disease controls. The study shown promising effect in lowering of body weight and by other pharmacological parameter. we concluded that ursolic acid derivative of *lantana camara* have a potent anti hyperlipidemic activity.

Keywords*: hyperlipidemia, lantana camara, ursolic acid*

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1. Introduction

Hyperlipidemia refers to elevated levels of Total cholesterol, TG, HDLs in the blood, and is also identified as dyslipidemia, to describe the manifestations of different disorders of lipoprotein metabolism.

Although elevated low density lipoprotein cholesterol (LDL) is thought to be the best indicator of atherosclerosis risk [1], Cholesterol, triglycerides, and phospholipids are the major lipids in the body. They are transported as complexes of lipid and proteins known as *lipoproteins*.

Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipid, free cholesterol, and protein and cores composed mostly of triglyceride and cholesterol ester [2]. It is major cause of atherosclerosis and atherosclerosis related condition like coronary heart disease (CHD), ischemic cerebrovascular disease, peripheral vascular disease and pancreatitis [3,4].

The etiology of hyperlipidemia can be classified into primary and secondary causes.

1. Primary due to [5]:
   - A single gene defect: is familial and called ‘monogenic’ or genetic and
   - Multiple genetic, dietary and physical activity related causes: ‘polygenic’ or malfactorial.
2. Secondary:
   - Associated with diabetes, myxoedema, nephritic syndrome, chronic alcoholism, drugs (corticosteroids, oral contraceptives, beta blockers).
   - Cholesterol and other fatty substances combine in the bloodstream and deposited in blood vessel forming plaque. Which leading obstruction of blood flow and causing heart attack, stroke and atherosclerois.

Lantana camara Linn. is regarded both as a notorious weed and a popular ornamental garden plant and posseses various uses in folk medicine in many parts of the world. [6] *Lantana camara*, also known as Spanish Flag or West Indian lantana, is a species of flowering plant in the verbena family; Verbenaceae. The plant has reported as anticonvulsant [7], anticancer [8,9], antiulcer [10], antioxidant [11], anti-diabetic [12,13], antifungal, antibacterial [14,15], anti-feedant, larval mortality/repellency [16,17], anti-motility [18], analgesic and anti-inflammatory [19] activities.

2. Material and Method

The fresh leaves of plant *Lantana camara* were collected from plant for extraction and then isolation of ursolic acid derivative from this plant with the help of column chromatography.

Albino rats of weighing 150-200 gm obtained from the animal house of the Faculty of Medicine, University of DIPSAR. Standard drug (atorvastatin) was purchased from local market.

3. Experimental Methodology

3.1. Experimental Methodology

The animals were kept in individual ventilated cages under the conditions of 22±25°C and a 12-hour light-dark cycle, with free access to food and water. The experimental protocol was approved by Institutional Animal Ethical Committee as per the guidance of committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India and approval no. is SIP/IAEC/09/2011.

The experimental design is depicted in the Figure 1 to Figure 3 below. In this experiment design following an acclimatization period of 4 weeks and 7 week study with purified diet, animals are divided in 6 groups, each group had 6 animals.

Group: 36 Animals will be divided in to 6 groups, 6 animals in each group.

Group 1: Normal

(animal study)

.......................1 week..........................12 weeks...............blood collect
(Acclimatization)

Group 2: Disease control High fat diet during whole study

(animal study)

................1week...........................12weeks...................blood collect
(Acclimatization) HFD

Figure 1. Group 1 normal & Group 2 disease control high fat diet

Group 3: High Fat Diet + Atorvastin

(Animal study)

..................1week............................12weeks.................blood collect
(Acclimatization) HFD+Atorvastin

Group 4: High Fat Diet + Ursolic Acid Derivative From Lantana Camara

(Animal study)

..................1week............................12weeks...............blood collect
(Acclimatization) HFD+test drug

Figure 2. Group 3: high fat diet+Atorvastin Group 4: high fat diet+Ursolic acid derivatives

Group 5: Normal Diet + Atorvastin

(Animal study)

.......................1week..............................12weeks..................blood collect
(Acclimatization) Normal diet+std. drug

Group 6: Normal Diet + Ursolic Acid Derivative From Lantana Camara

(Animal study)

.......................1week.............................12weeks..................blood collect
(Acclimatization) Normal diet+test drug

Figure 3. Group 5: Normal Diet + Atorvastin & Group 6: Normal Diet + Ursolic acid Derivative

3.1. Evaluation Parameters

- Body weight variation
- Lipid profile parameters: Cholesterol, Triglyceride, LDL, HDL, VLDL.
- Liver function tests: Bilirubin (direct, indirect), SGOT, SGPT, Alkaline phosphatase, Total protein, albumin, globulin, GGT.
- Hematology**:** HB, TLC, TRBC, PCV, Platelets count, ESR, lipase.

3.2. Blood Sampling and Serum Extraction

Blood was collected from all groups directly from retro orbital plexus after anaesthetization by a mixture of cholroform-ether (2:3) at the end of protocol period. Serum was separated after coagulating blood for 30 min. and centrifuged at 1500 rpm for 20 min., serum was then separated and was used for estimation of biochemical parameters.

3.3. Statistical Analysis

All the data is expressed as mean± S.E.M .Significant difference between the mean values were statistically analyzed using one ay analysis of variance. the values less than 0.001 were considered significant.

4. Results and Discussion

4.1. Variation of Body Weight

The observation of biological parameters in the body weight of rats, there is slight increased in the body weight of all rats in drug controlled, in comparison of HFD+STD, HFD+TD, ND+STD, ND+TD increased and NC is decreased.

Table 1. Weight variation chart after treatment: As comparison to drug controlled group (All the data expressed are mean ± s.e.m. With each group having six animals each: a=compared to drug controlled group.,*=p<0.0001%, ns=not significant)**

s.no.	Groups	Body weight(gm)
1.	Normal controlled	156.7±6.667
2.	Drug controlled	218.7±5.270
3.	High fat diet + std. Drug	155.8±7.538$^{a/***}$
4.	High fat diet+ test drug	141.7±6.086$^{a/***}$
5.	Normal diet + std. Drug	134.2±4.785$^{a/***}$
6.	Normal diet+ test drug	151.3±9.149$^{a/***}$

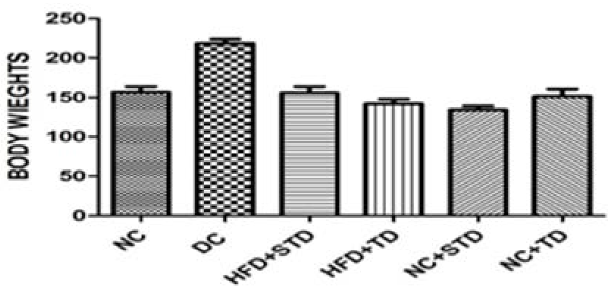

Figure 4. Body weight variation after treatment in different groups

4.2. Blood Examination Report

Haemoglobin reports: Haemoglobin level is very slightly increases in drug controlled group comparison to others groups.

Table 2. All the data expressed are mean±s.e.m. Witheach froup having six animals each. a=compared to drug controlled group. ***=p<0.0001%, ns=not significant.

s.no.	Groups	HBgm%
1.	NC	12.87±0.3278$^{a/ns}$
2.	DC	13.88±0.3270
3.	HFD+STD	12.95±0.2460$^{a/ns}$
4.	HFD+TD	13.32±0.3250$^{a/ns}$
5.	ND+STD	13.35±0.2895$^{a/ns}$
6.	ND+TD	13.40±0.2781$^{a/ns}$

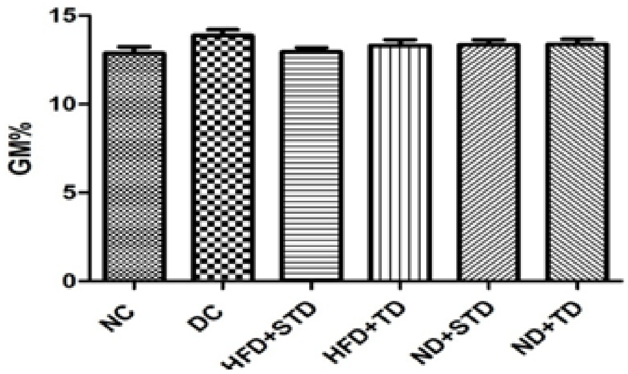

Figure 5. Heamoglobin levels in each groups

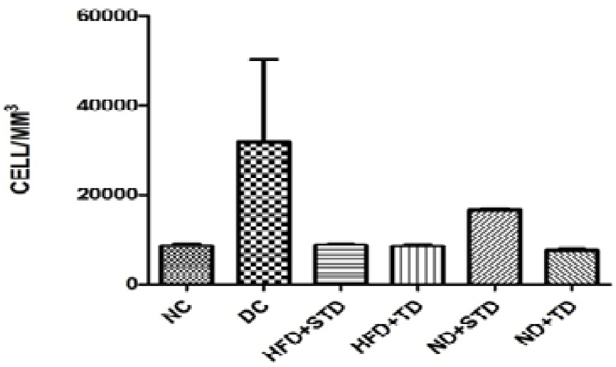

Figure 6. Total leukocyte count levels in different groups

TLC Blood Test Report: The levels of TLC in DC and ND+STD is slightly increased as comparison to NC, HFD+STD, HFD+TD, ND+TD.

Table 3. All the data expressed are mean±s.e.m. Witheach froup having six animals each.,a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no.	Groups	TLC Cell/mm^3
1.	NC	8550±437.2$^{a/ns}$
2.	DC	31733±0.3270
3.	HFD+STD	8733±244.8$^{a/ns}$
4.	HFD+TD	8467±360.2$^{a/ns}$
5.	ND+STD	16483±490.9$^{a/ns}$
6.	ND+TD	7467±261.6$^{a/ns}$

Trbc Reports: The TRBC level in ND+TD, is slightly increases as comparison to DC, and others groups having almost same values.

Table 4. All the data expressed are mean±s.e.m. With each group having six animals each.,a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no.	Groups	TRBC Million/mm^3
1.	NC	7.087±0.03127$^{a/***}$
2.	DC	7.535±0.1004
3.	HFD+STD	7.150±0.04163$^{a/***}$
4.	HFD+TD	7.108±0.03710$^{a/***}$
5.	ND+STD	7.120±0.02671$^{a/***}$
6.	ND+TD	7.328±0.04483$^{a/ns}$

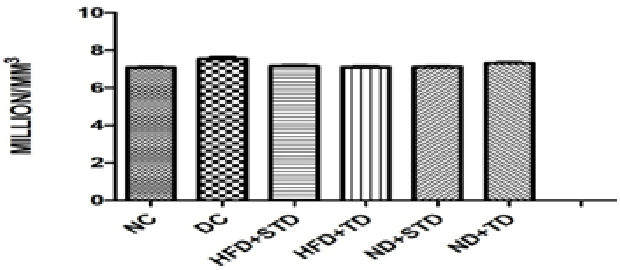

Figure 7. Total red blood cell in different groups

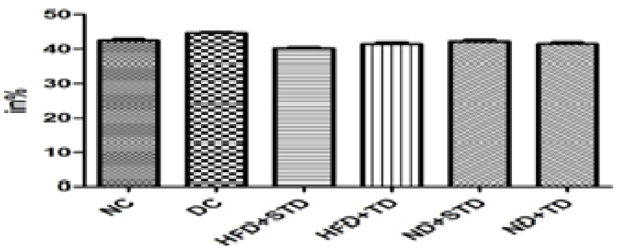

Figure 8. Haematocritvalues in different groups

Packed Cell Volume Report: Packed Cell Volume is slightly increases comparison to DC.

Table 5. All the data expressed are mean±s.e.m. With each groups having six animals each. a=compared to drug controlled group., ***=p<0.0001%, ns=not significant.

S.No.	Groups	PCV%
1	NC	42.5±0.5930$^{a/*}$
2	DC	44.90±0.2817
3	HFD+STD	40.18±0.2774$^{a/***}$
4	HFD+TD	41.53±0.5038$^{a/***}$
5	ND+STD	42.28±0.5486$^{a/*}$
6	ND+TD	41.58±0.4672$^{a/***}$

Platelet count report: Platelets Count in HFD+STD and ND+TD is increases when compared to NC and DC.

Table 6. All the data expressed are mean±s.e.m. With each group having six animals each., a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

S.No.	Groups	Platelet count/mm^3
	NC	5696±10194$^{a/ns}$
	DC	551167±9864
	HFD+STD	757167±7016$^{a/*}$
	HFD+TD	621083±109565$^{a/*}$
	ND+STD	550667±4602$^{a/ns}$
	ND+TD	729667±4800$^{a/ns}$

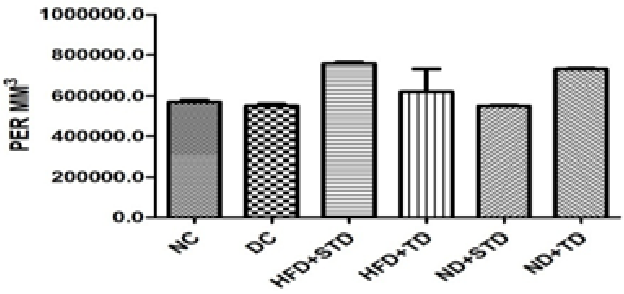

Figure 9. Platelet count in different groups

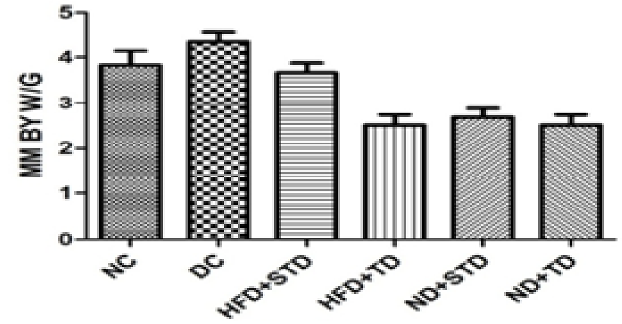

Figure 10. ESR values in different groups

ESR REPORT: Levels of ESR decreases HFD+TD , ND+STD, ND+TD when comparison to NC but in DC it is slightly increased.

Table 7. All the data expressed are mean±s.e.m. With each group having six animals each., a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no.	Groups	ESR Mm by w/g
1.	NC	3.83±0.3073$^{a/ns}$
2.	DC	4.333±0.2108
3.	HFD+STD	3.667±0.2108$^{a/ns}$
4.	HFD+TD	2.500±0.2236$^{a/***}$
5.	ND+STD	2.667±0.2108$^{a/***}$
6.	ND+TD	2.500±0.2236$^{a/***}$

Lipase Report: The level of lipase in DC is increased as comparison to others groups.

Table 8. All the data expressed are mean±s.e.m. With each group having six animals each.,a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

S.No	Groups	Lipase u/l
1.	NC	566.7±7.149$^{a/***}$
2.	DC	848.3±6.009
3.	HFD+STD	566.7±5.578$^{a/***}$
4.	HFD+TD	564.5±4.365$^{a/***}$
5.	ND+STD	537.0±8.177$^{a/***}$
6.	ND+TD	580.8±5.406$^{a/***}$

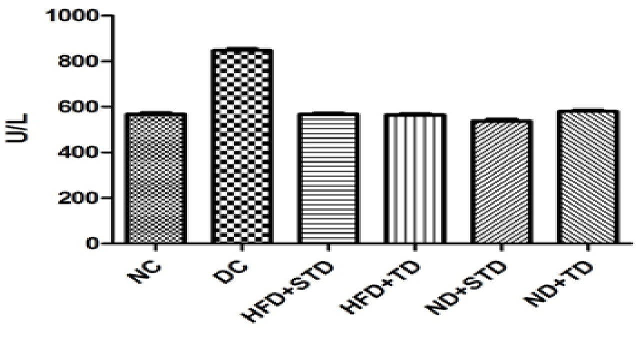

Figure 11. Lipase activity in different groups

Table 9. All the data expressed are mean±s.e.m. Witheach froup having six animals each., a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no	Groups	Cholesterol	Triglyceride	HDL	LDL	VLDL
1	NC	107.2±1.470$^{a/ns}$	102.5±0.6708$^{a/**}$	23.67±0.4216$^{a/***}$	51.33±0.4944$^{a/***}$	22.33±0.333$^{a/ns}$
2	DC	106.0±1.238	108.7±0.6146	26.83±0.5426	61.33±0.4216	23.83±0.3073
3	HFD+STD	112.2±10815$^{a/*}$	117.2±0.8724$^{a/***}$	29.83±0.4773$^{a/***}$	66.17±0.4014$^{a/***}$	22.00±0.5774$^{a/ns}$
4	HFD+TD	115.7±1.476$^{a/***}$	101.3±0.4944$^{a/***}$	27.50±0.4282$^{a/ns}$	66.00±0.365$^{a/***}$	23.83±0.3073$^{a/ns}$
5	ND+STD	105.7±0.5578$^{a/ns}$	100.7±1.453$^{a/***}$	27.33±0.333$^{a/ns}$	57.83±0.4773$^{a/***}$	19.83±0.6009$^{a/***}$
6	ND+TD	106.8±0.6009$^{a/ns}$	109.7±1.430$^{a/ns}$	28.33±0.4944$^{a/ns}$	58.33±0.333$^{a/***}$	19.50±0.4282$^{a/***}$

Lipid profile test: The level of triglyceride in HFD+STD is slightly increased as compared to DC. The level of HDL slightly increased in HFD+STD as comparison to others groups. LDL level is increased in HFD+ STD,HFD+TD as comparison to DC. VLDL is slightly increased in DC and HFD +TD but the level of ND+STD, ND+TD is slightly decreased.

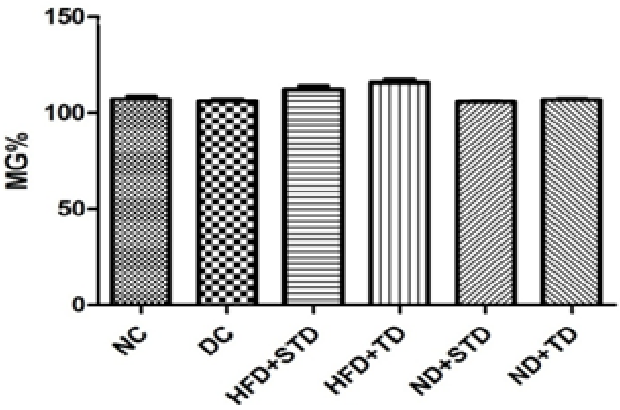

Figure 12. Cholesterol level in different groups

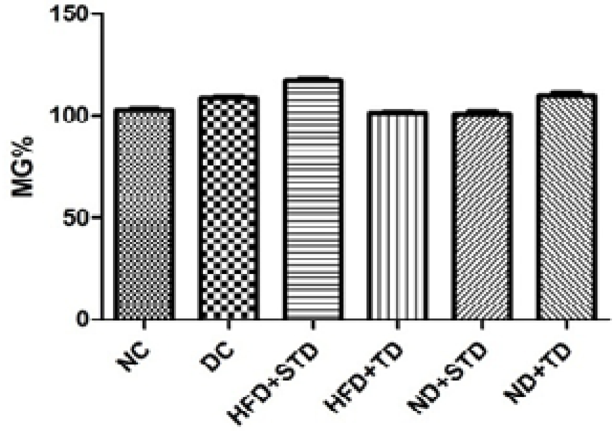

Figure 13. Triglycerides levels in each groups

Liver functions tests:

SGOT level is slightly increases in DC as comparison to others groups. SGPT slightly increased in the DC as compared to the HFD+STD, HFD+TD, ND+STD, ND+TD. Alkaline Phosphatase level of DC increased and the level of HFD+STD,HFD+TD,ND+STD is slightly increased. The level of GGT in DC group is increased and the level of HFD+TD, ND+STD and ND+TD is slightly decreased.

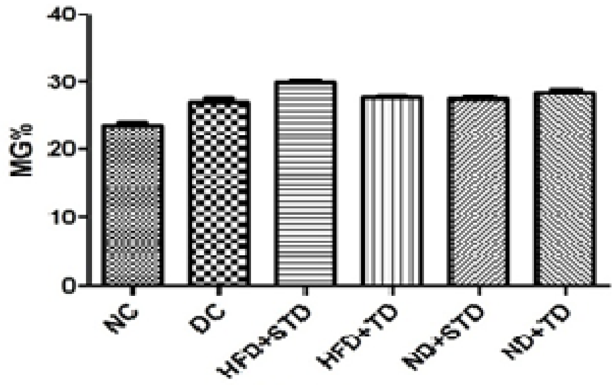

Figure 14. HDL levels in different groups

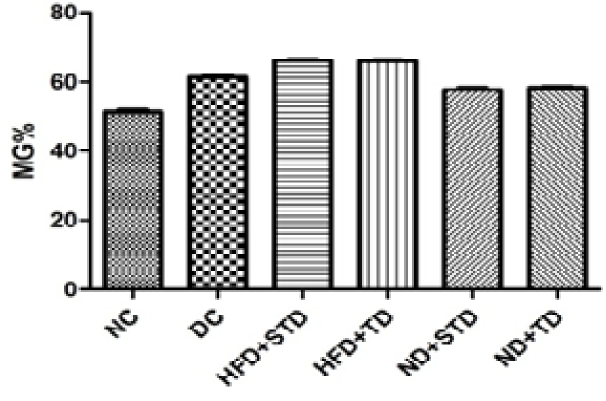

Figure 15. LDL levels in different groups

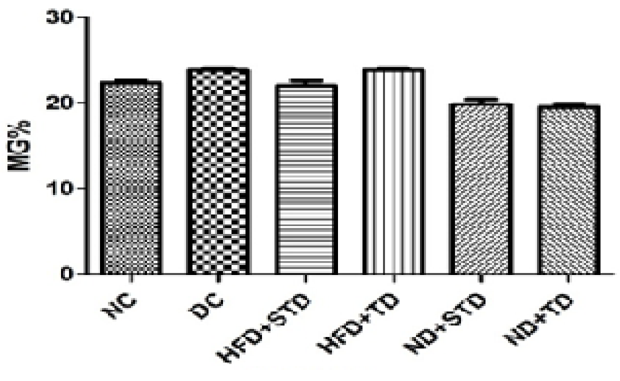

Figure 16. VLDL levels in different groups

Table 10. All the data expressed are mean±s.e.m. With each group having six animals each., a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no.	Groups	Bilirubin	Direct	Indirect
1	NC	0.3833±0.003333$^{a/**}$	0.1783± 0.00307$^{a/*}$	0.2100±0.0036$^{a/ns}$
2	DC	0.4033± 0.003333	0.1950±0.002236	0.2167±0.0033
3	HFD+STD	0.4083± 0.003073$^{a/ns}$	0.2033±0.00210$^{a/ns}$	0.2167±0.0033$^{a/ns}$
4	HFD+TD	0.4517± 0.004014$^{a/***}$	0.2150± 0.00428$^{a/**}$	0.2367±0.0061$^{a/*}$
5	ND+STD	0.4567± 0.003333$^{a/***}$	0.2000± 0.00365$^{a/ns}$	0.2050±0.0022$^{a/ns}$
6	ND+TD	0.3950± 0.004282$^{a/ns}$	0.2017±0.00477$^{as/ns}$	0.2433±0.0033$^{a/***}$

Table 11. All the data expressed are mean±s.e.m. With each group having six animals each., a=compared to drug controlled group., ***=p<0.0001%, ns=not significant

s.no.	Groups	Sgot	Sgpt	Alkaline phosphatase	GGT
1	NC	141.5±3.862$^{a/ns}$	139.3±5.506$^{a/***}$	368.2±34.53$^{a/ns}$	53.33±1.626$^{a/***}$
2	DC	154.0±2.503	178.8±2.868	403.8±5.256	68.67±0.8433$^{a/***}$
3	HFD+STD	147.5±3.008$^{a/ns}$	166.0±2.129$^{a/ns}$	353.0±9.363$^{a/ns}$	48.83±1.167$^{a/***}$
4	HFD+TD	139.0±5.989$^{a/ns}$	148.7±3.190$^{a/***}$	364.5±14.53$^{a/ns}$	49.83±0.9458$^{a/***}$
5	ND+STD	128.7±1.606$^{a/***}$	152.7±2.704$^{a/***}$	310.5±17.37$^{a/ns}$	43.33±0.9189$^{a/***}$
6	ND+TD	101.7±4.780$^{a/***}$	119.0±5.756$^{a/***}$	355.7±40.17$^{a/ns}$	35.17±0.5426$^{a/***}$

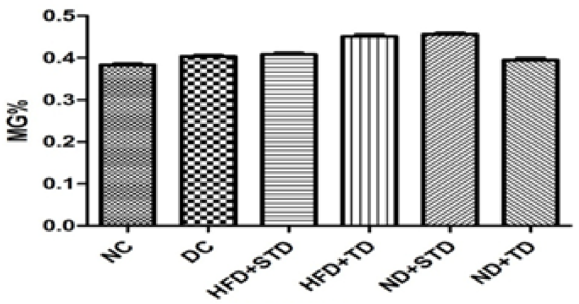

Figure 17. Bilirubin level in different groups

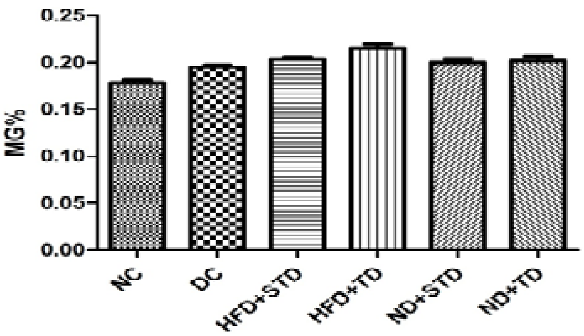

Figure 18. Direct level in different groups

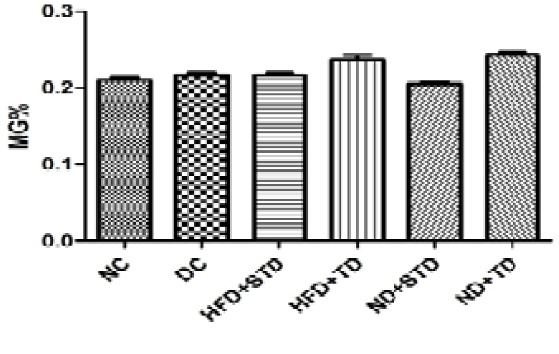

Figure 19. Indirect level in different groups

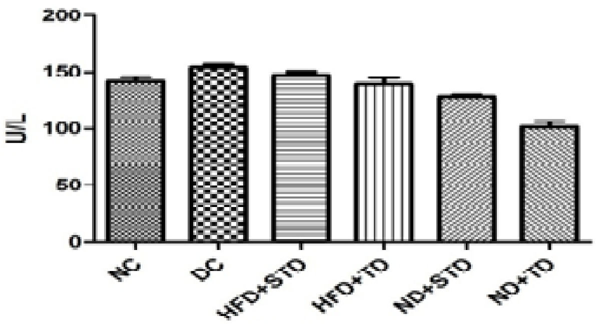

Figure 20. SGOT level in different groups

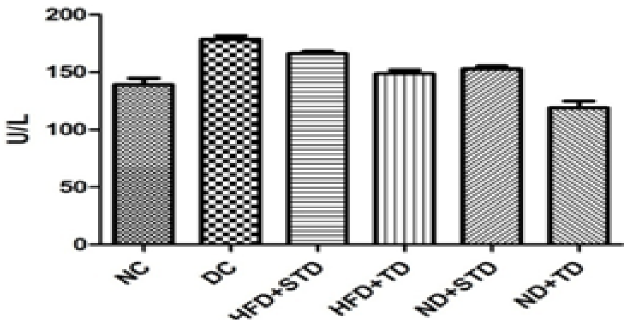

Figure 21. SGPT level in different groups

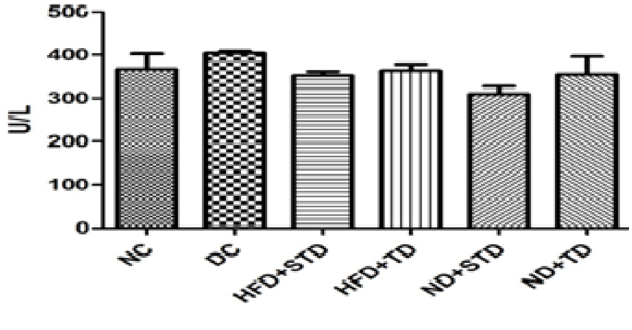

Figure 22. ALKALINE PHOSPHATASE in different groups

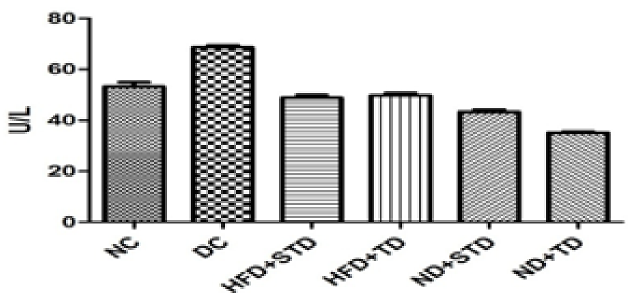

Figure 23. GGT level in different groups

Mortality: None of the animals have died from any of the groups before termination of the experimental termination.

5. Conclusion

The present study provides evidence for the ability of UASG, to decreased the lipid levels of high fat diet induced hyperlipidemia in **wistar** rats. The UASG also subjected to a toxicity testing and it was tested up to a high concentration of 10 mg /kg, orally(3 times per day) evaluated in the present study . Even at this dose the extract did not produce signs of toxicity or treatment related adverse effects in the tests for anti hyperlipidemia activity. This study clearly suggests that UASG is a potent hypolipidemic in rats.

Abbreviation

CHD	Coronary Heart Disease
LDL	low density lipoprotein
HDL	high density lipoprotein
VLDL	very low density lipoprotein
USAG	Ursolic acid steroyl glucoside
DIPSAR	delhi institute ofpharaceutical science and research
CPCSEA	committee for the purpose of Control and Supervision of Experiments on Animals
IAEC	instutional animal ethical committe
NC	normal controlled
DC	drug controlled
STD	standard drug
TD	test drug
ND	normal diet
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum gutamic pyruvic transamnase
GGT	gamma-glutamyl transpeptide
Hb	haemoglobin
TLC	total leukocyte count
TRBC	total red blood cell
PCV	packed cell volume
ESR	erythrocyte sedimentation rate
SEM	standard error mean

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