International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 4 | Issue 1 | Jan - Jun - 2020
www.ijpcr.net

Research article *Clinical research*

ISSN: 2521-2206

Evaluation of anti Hyperlipedimic activity of Amaranthus extract in experimental animal model

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ABSTRACT

Objective

To investigate the anti diabetic and anti Hyperlipidemic activity of methanol extract of Amaranthus in male Wistar rats.

Material & method

In this model of Hyperlipidemia, 30 adult male wistar rats (150-200gms) were evenly divided into 5 groups in both groups. Group-1 and Group-2 served as untreated and model controls respectively, while Group-3, 4 and 5 were the treatments groups which were simultaneously treated with standard, 200 and 400 mg/kg extract respectively along with High Fat Diet and Triton x 100. On last day, blood samples for biochemical parameters, were obtained under inhaled diether anaesthesia.

Results

HFD and Triton x 100 treatment caused Hyperlipidemia as evidenced by marked elevation in Cholesterol, Triglycerides, LDL, VLDL and decrease in HDL levels. Co-administration of extract with HFD and Triton x 100 decreased rise Cholesterol, Triglycerides, LDL, VLDL and increase in HDL levels.

Conclusion

It was observed that the methanol extract of ***Amaranthus*** conferred Anti- Hyperlipidemia activity by biochemical observation against HFD and Triton-x-100 induced Hyperlipidemia in rats. In the near future could constitute a lead to discovery of a novel drug for treatment of drug induced Hyperlipidemia.

Keywords: ***Amaranthus,*** Anti- Hyperlipidemia activity.

INTRODUCTION

Hyperlipidemia is a condition when abnormally high levels of lipids i.e. The fatty substance are found in the blood. This condition is also called hypercholesterolemia/ hyperlipoproteinemia [1]. Human body is complex machinery and for maintaining the homeostasis of various organ and organ system. Any undesirable change will disturb the balance resulting in diseased state [2]. Lipids are fats in the blood stream, commonly divided into cholesterol and triglycerides. Cholesterol circulates in the bloodstream and is involved in the structure and function of cells. Triglycerides (TG) are best viewed as energy that is either used immediately

or stored in fat cells.TG are manufactured in the liver from the foods or by being absorbed from the intestine [3]. Virchow in 19th century who identified cholesterol crystals in atherosclerotic lesion and stated that endothelial cell injury initiates atherogenesis2. In a modification of this hypothesis it was proposed that the endothelium normally influences the behavior of arterial smooth muscle cells by providing a barrier to the passage of plasma proteins, and that the major effect of haemodynamic or other factors that injure endothelium is to reduce the effectiveness of the barrier [4]. Arteries are normally smooth and unobstructed on the inside, but in case of increased lipid level, a sticky substance called plaque is formed inside the walls of arteries. This leads to reduced blood flow, leading to stiffening and narrowing of the arteries. It has been proved that elevated plasma levels of cholesterol and of LDL are responsible for atherosclerosis in man, and epidemiological data suggests that elevated plasma levels of HDL have a protective effect [5].

MATERIALS AND METHODS

Plat material

The leaves of plant *Amaranthus* was collected from hilly region of chittoor district, Tirupathi, A.P, India. The plant was authenticated by Dr. K. Madhav Chetty, Asst. Professor, Dept. of Botany, Sri Venkateshwara University, Tirupathi.

Experimental animals

Male Wistar rats weighing (180-220g) were provided by animal house of Sigma Institute of Clinical Research and Administration (SICRA Labs), Kukatpally, Hyderabad, India. They were housed in ventilated rooms at a temperature of 24±2°c with a 12h light/dark cycle and 54±5% relative humidity, maintained on standard pellet and water ad libitum throughout the experimental period. The animals were acclimatized for a period of one week. The experiments were carried out according to the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA), New Delhi, India and approved by the Institutional Animal Ethical Committee (IAEC) of Sigma Institute of Clinical Research and Administration pvt. ltd. Hyderabad.

Drugs and chemicals

Amaranthus, all other chemicals and diagnostic kits were provided by Sigma Institute of Clinical Research and Administration.

Phytochemical screening

Preliminary phytochemical investigation was carried out on Methanol extract of *Amaranthus* leaf for detection of various phytochemicals by standard methods [6]

Determination of acute oral toxicity

Acute toxicity studies were performed according to OECD-423 guidelines category IV substance (acute toxic class method). Albino rats (n=3) of either sex selected by random sampling technique were employed in this study. The animals were fasted for 4 hrs with free access to water only. The plant extracts of *Amaranthus* were administered orally with maximum dose of 2000 mg/kg body weight. The mortality was observed for three days. If mortality was observed in 2/3 or 3/3 of animals, then the dose administered was considered as a toxic dose. However, if the mortality was observed only one rat out of three animals then the same dose was repeated again to confirm the toxic effect. If mortality was not observed, the procedure was then repeated with higher dose (Organization for economic Co-operation and development, 2001).

Experimental animals

Wistar albino adult male rats weighing 200-250g were obtained from the animal house. The animal were grouped and housed in polyacrylic cages (38x 23x 10 cm) with not more than five animals per cage and maintained under standard laboratory under standard laboratory conditions (temperature 25+2oC) with dark and light cycle (14/10 hour). They were allowed free access to standard dry pellet diet (Hindustan Lever, Kolkata, India) and water ad libitum. The mice were acclimatized to laboratory condition for 10 days before commencement of experiment. The experimental protocol was approved by Institutional Animal Ethical Committee (IAEC) constituted under CPCSEA.

Induction of Hyperlipidemia by Triton-x-100

Hyperlipidemia was induced in Wistar albino rats by single intraperitoneal injection of freshly

prepared solution of Triton-X-100 (100 mg/kg) in physiological saline solution after overnight fasting for 18 h [7].

The animals were divided into five groups of six rats each.

1. The first group was given standard pellet diet, water and orally administered with 2% Tween 80.
2. The second group was given a single dose of triton administered at a dose of 100mg/kg, i.p. After 72 hours of triton injection, this group received a daily dose of 2% Tween 80 (p.o) for 7 days.
3. The third group was administered a daily dose of Atorvastatin 10 mg/day
4. Fourth group Amaranthus200mg/kg suspended in 2% Tween 80, p.o., for 7 days, after inducing hyperlipidemia.
5. Fifth group was administered with the Amaranthus400 mg/kg, p.o. for 7 days [8].

Induction of Hyperlipidemia by High Fat Diet

The animals were divided into five groups. Each group contains six animals.

Grouping is as follows:

Group 1: Normal Group (Tween 80)

Group 2: Control Group (HFD)

Group 3: Standard-Atorvastatin + HFD (10 mg/kg)

Group 4: Extract II- *Amaranthus*+ HFD (400 mg/kg)

Group 5: Extract I- *Amaranthus*+ HFD (200 mg/kg)

The study Duration is 14 days

Collection of blood

On the 8thday, blood was collected by retro orbital sinus puncture, under mild ether anaesthesia. The collected samples were centrifuged for 10 minutes. Then serum samples were collected and used for various biochemical experiments. The animals were then sacrificed and the liver collected [9].

RESULTS AND DISCUSSIONS

Evaluation of Anti Hyperlipidaemic activity of *Amaranthus* in Rats

Mean and S.E.M of parameters of the animals

Table 6.5: TRITON-X-100 Induced Model

Triton x-100					
TEST	**NORMAL**	**CONTROL**	**STANDARD**	**T1**	**T2**
ALP	74.59±3.107	162.51±1.34***	125.78±1.52***	126.23±0.92***	78.2±1.423
GPT	35.26±1.275	65.80±1.413***	41.11±3.826	40.79±1.385***	35.71±1.671**
GOT	41.50±3.226	53.70±3.894*	41.68±2.426	42.35±2.310	46.32±2.075
TP	40.31±3.128	32.71±1.751***	19.56±2.321***	16.26±2.315***	22.89±1.483***
HDL	53.48±3.652***	23.82±1.516	41.69±3.971**	51.25±2.153	56.85±2.351
TG	51.12±2.128	81.76±1.621***	79.23±1.619***	81.2±2.210***	61.42±3.126***
TC	66.35±2.328	151.01±2.121***	68.05±1.451	98.52±1.612***	92.21±1.811***
VLDL	10.01±0.233	15.59±0.627***	13.85±0.352***	15.45±0.356***	13.30±1.464***
LDL	11.56±2.692	101.63±5.069***	10.63±3.114	33.83±4.159	21.98±2.700
AI	0.41±0.239	3.29±0.358	0.42±0.189	0.96±0.328	0.51±0.496
CRR	3.12±0.521	7.63±0.491	2.68±0.122	2.23±0.214	2.16±0.161

Table 6.6 Body Weight

TRITON X100	**NORMAL**	**CONTROL**	**STANDARD**	**T1**	**T2**
Before treatment	173.0±0.96	172.66±0.89	174.0±1.12	173.33±0.88	172.0±0.85
After treatment	183.5±0.76	243.0±0.96***	194.33±0.66***	224.33±0.88***	244.83±1.14***

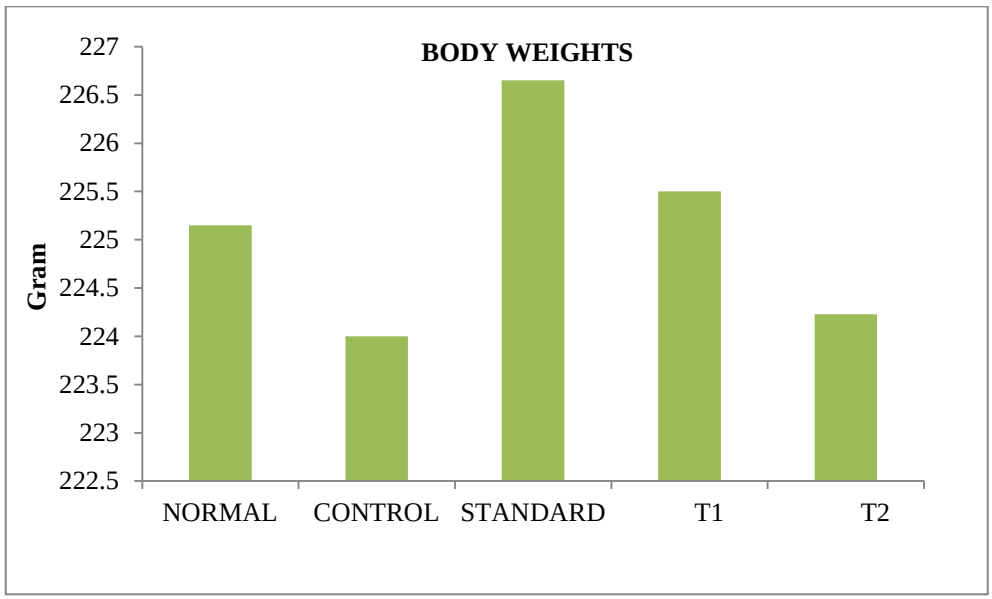
N = 6; Significance: *** $P<0.001$, ** $P<0.01$, * $P<0.05$ from control

HFD diet induced model

Table no 6.7: Biochemical Parameters of the Animals

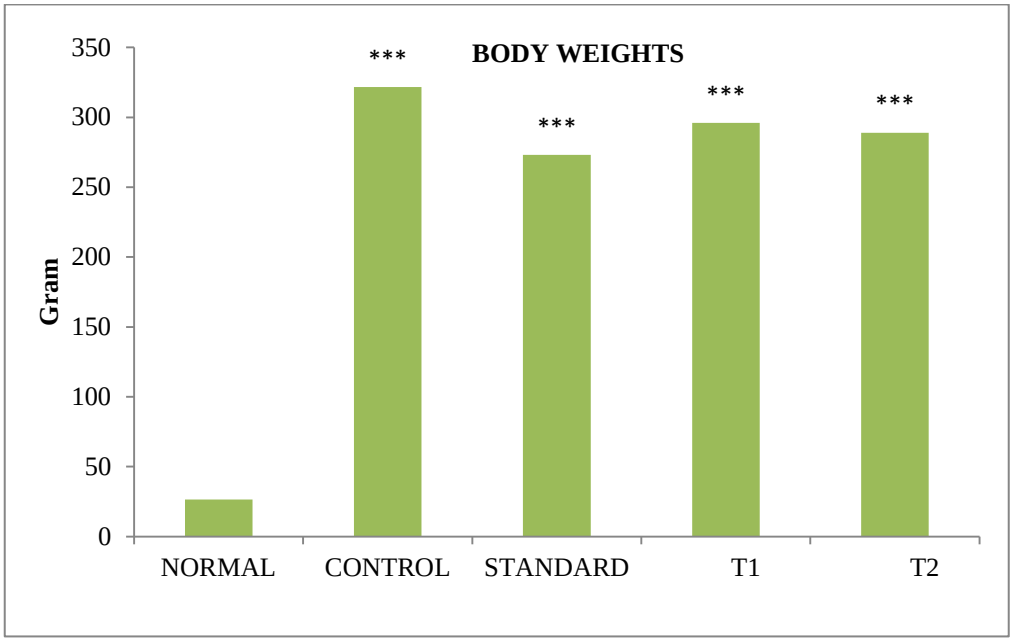
HFD diet	NORMAL	CONTROL	STANDARD	T1	T2
B.w B.T	231.28±0.1	213±1.06	218.59±2	238.7±0.43	231.12±0.61
B.w A.T	25.4±0.15	342.61±2.4***	251.29±0.5***	221.43±2.71***	269±2.75***
HDL	26.12±0.23	21.5±0.83**	33.19±0.54**	32.23±0.47**	36.87±0.10***
LDL	25.19±0.56	56.40±0.10***	35.85±0.26***	41.17±1.43***	26.28±1.69
VLDL	13.10±2.63	20.72±0.58***	14.38±0.59***	13.76±0.48	14.22±0.52
GLUCOSE	72.43±0.81	151.2±0.60***	107.1±0.75***	124.1±0.47***	108.1±0.70***
TC	64.02±0.51	102.0±0.19***	86.1±0.60***	81.25±2.55***	65.43±0.39
TG	52.05±1.15	92.01±0.24***	60.94±2.11***	71.55±2.46***	52.89±0.75
AI	1.41±0.574	3.67±0.529***	1.66±0.619	1.69±0.46	0.77±0.98***
CRR	2.21±0.218	3.57±0.529***	2.98±0.328	2.31±0.85	1.75±0.89***

Triton-X-100 induced Hyperlidaemia model

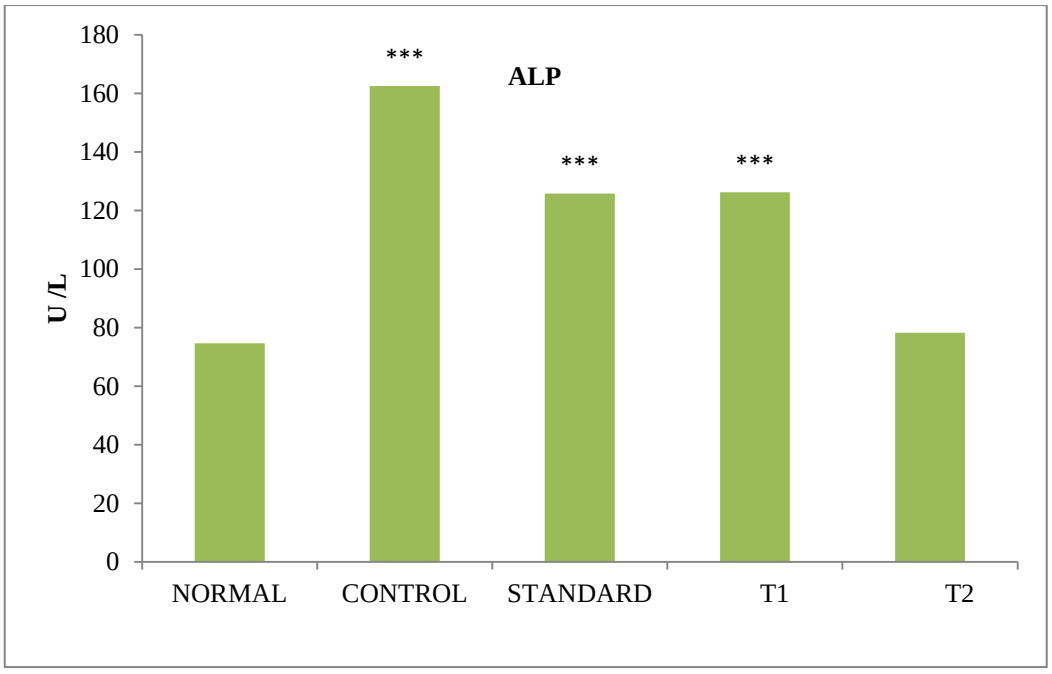


Graph 2 Histogram showing Initial BODY WEIGHT of animals

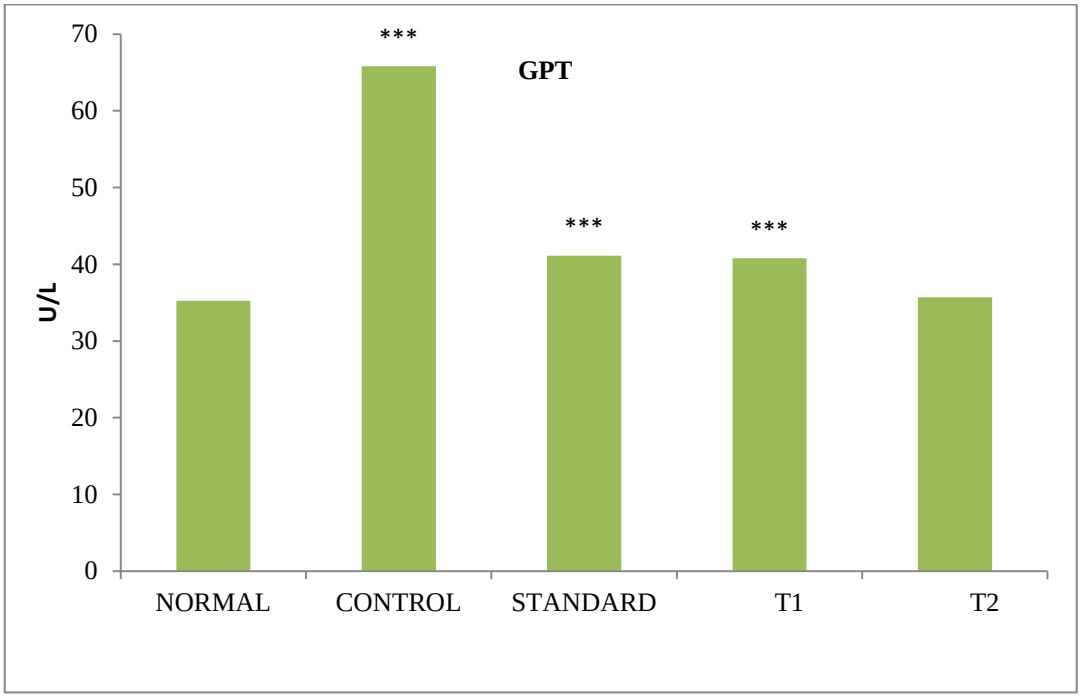
N = 6; Significance: *** $P<0.001$, ** $P<0.01$, * $P<0.05$ from control



Graph 3 Histogram showing the effect of *Amaranthus* on BODY WEIGHT of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control

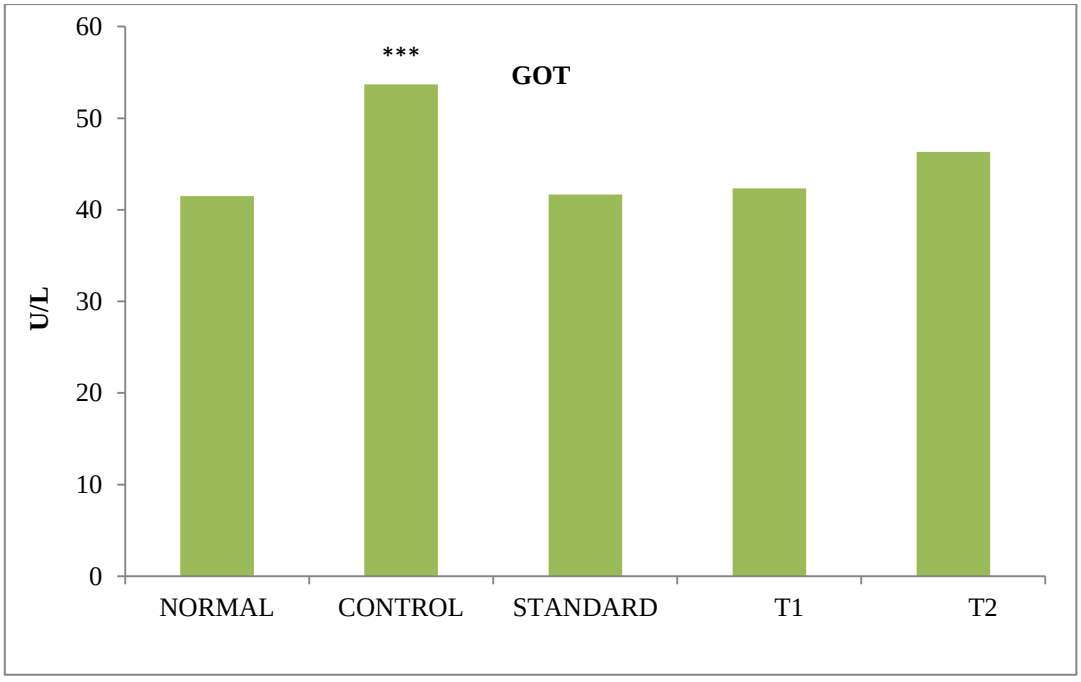


Graph 4 Histogram showing the effect of *Amaranthus* on ALP of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



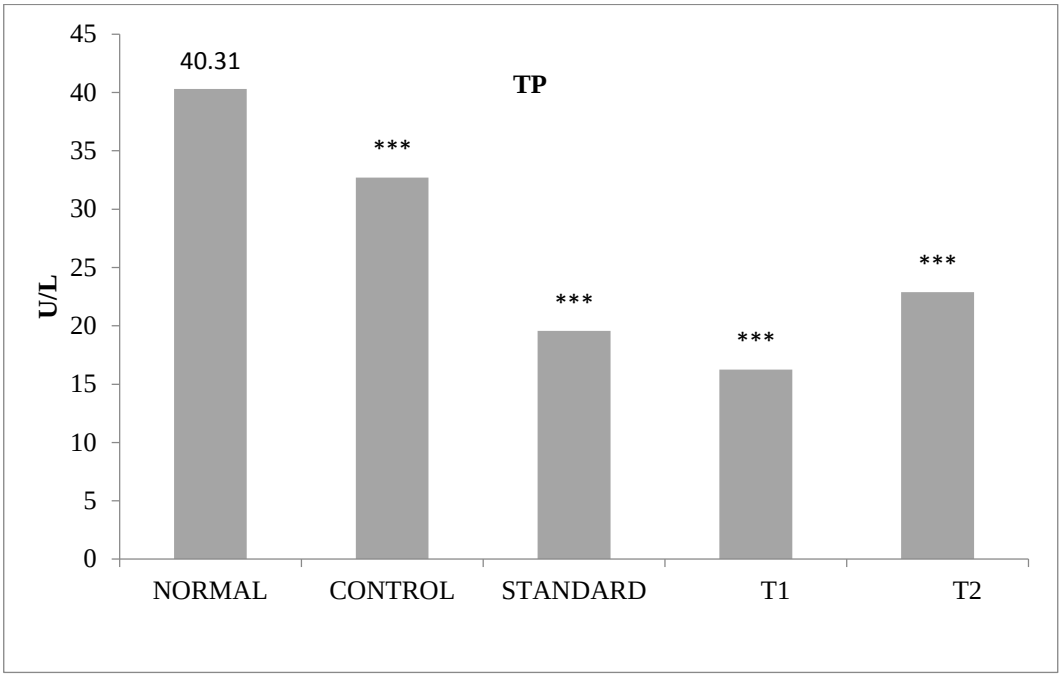
Graph 5 Histogram showing the effect of *Amaranthus* on SGPT of animals

N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



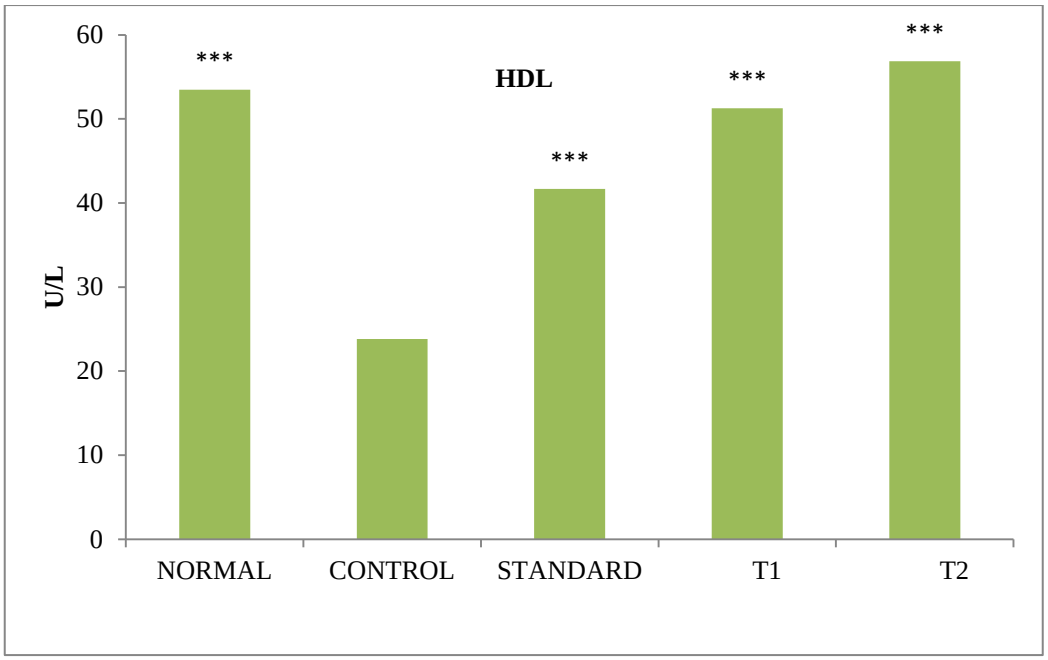
Graph 6 Histogram showing the effect of *Amaranthus* on SGOT of animals

N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



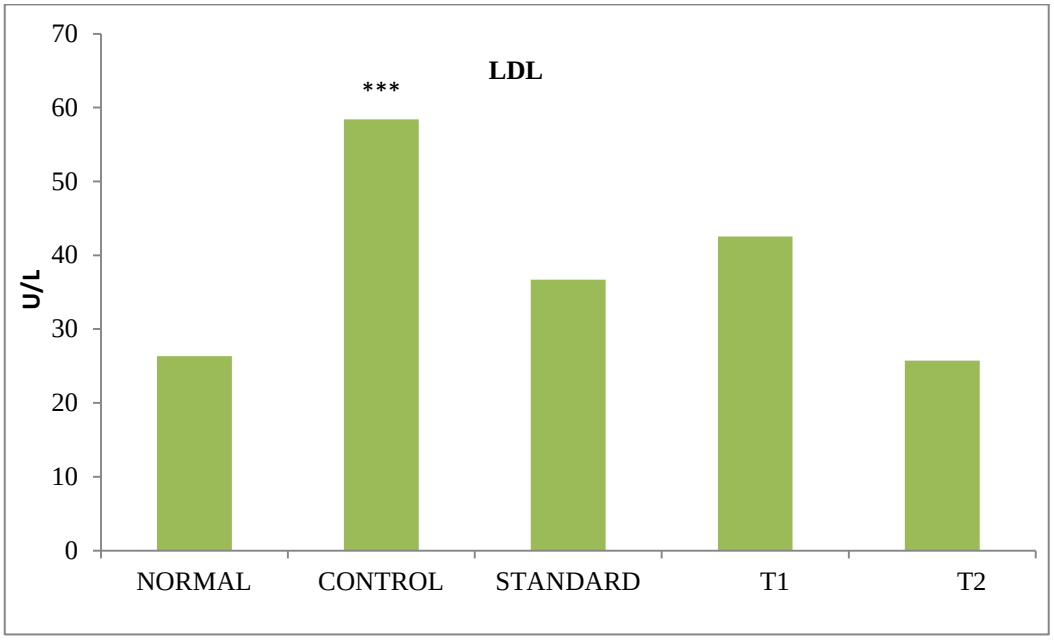
Graph 7 Histogram showing the effect of *Amaranthus* on Total protein of animals

N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control

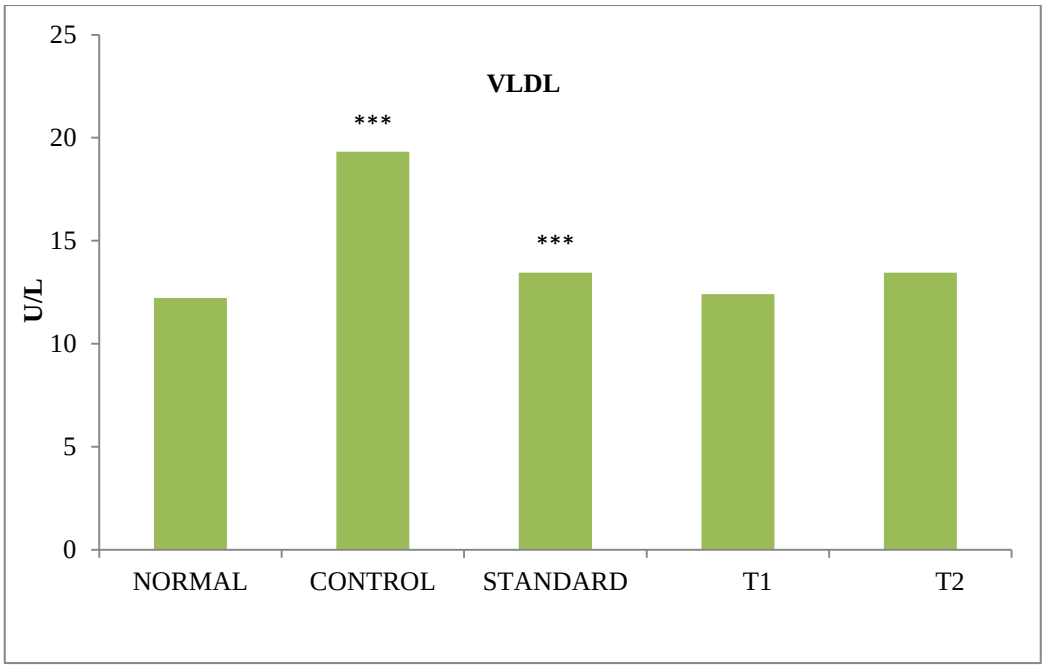


Graph 8 Histogram showing the effect of *Amaranthus* on HDL of animals

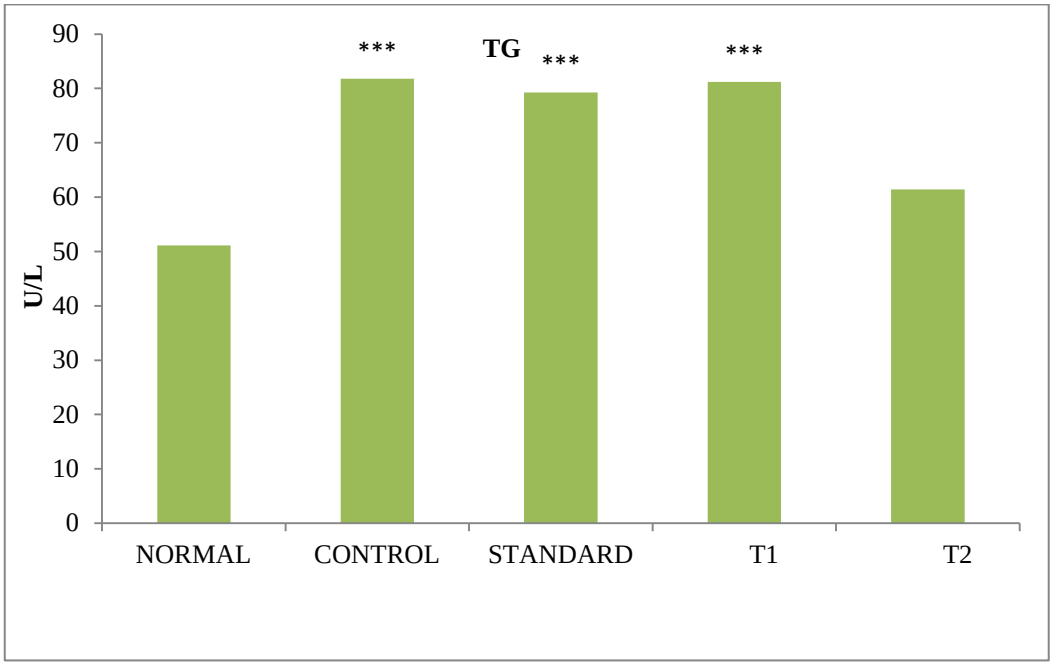
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



Graph 9 Histogram showing the effect of *Amaranthus* on LDL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control

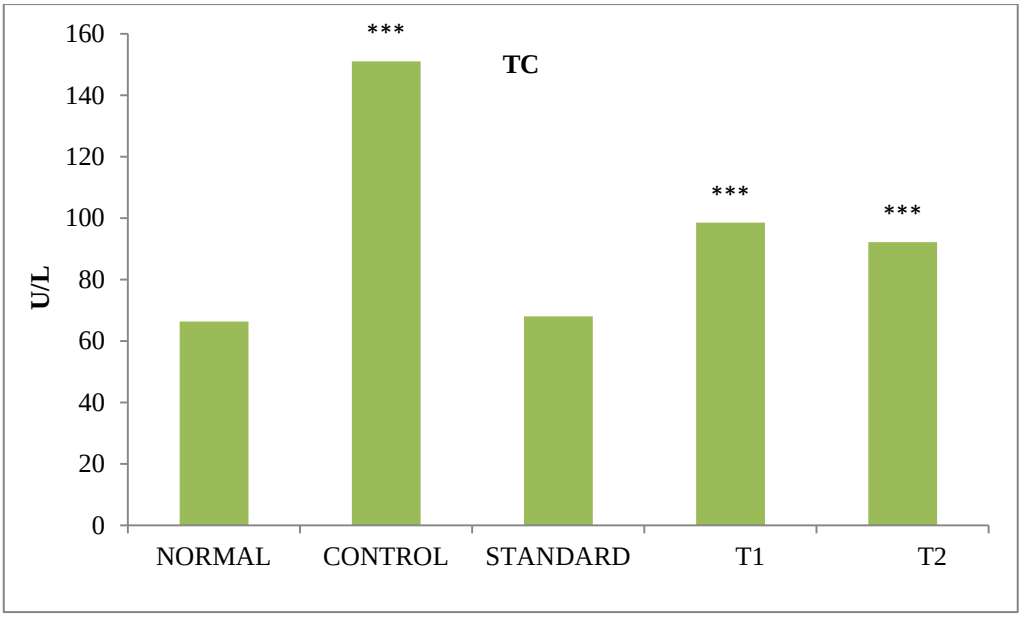


Graph 10 Histogram showing the effect of *Amaranthus* on VLDL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



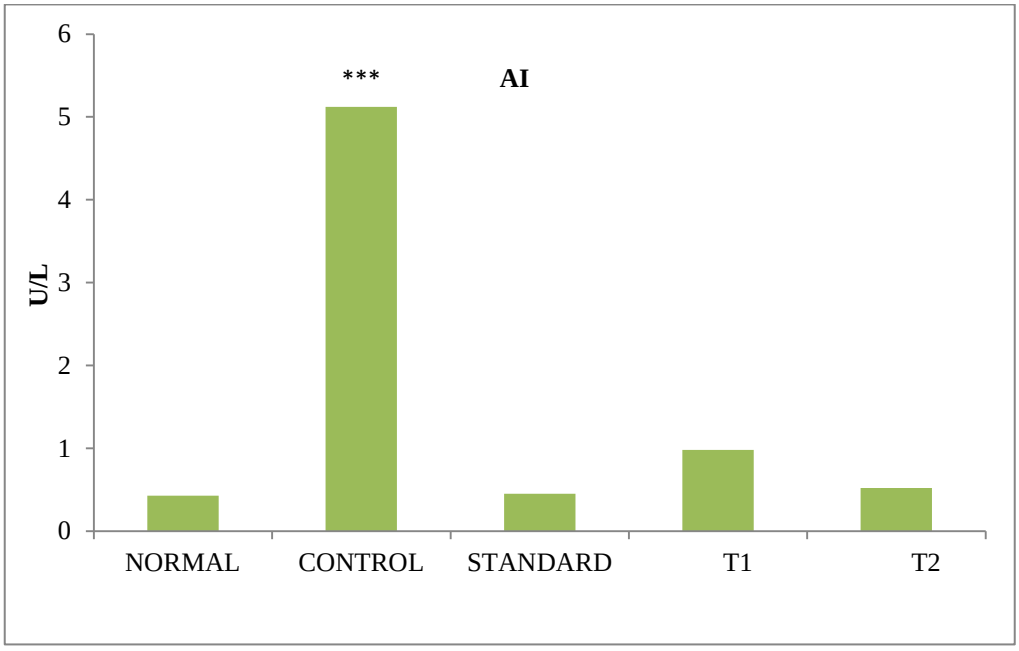
Graph 11 Histogram showing the effect of *Amaranthus*Triglycerides of animals

N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control

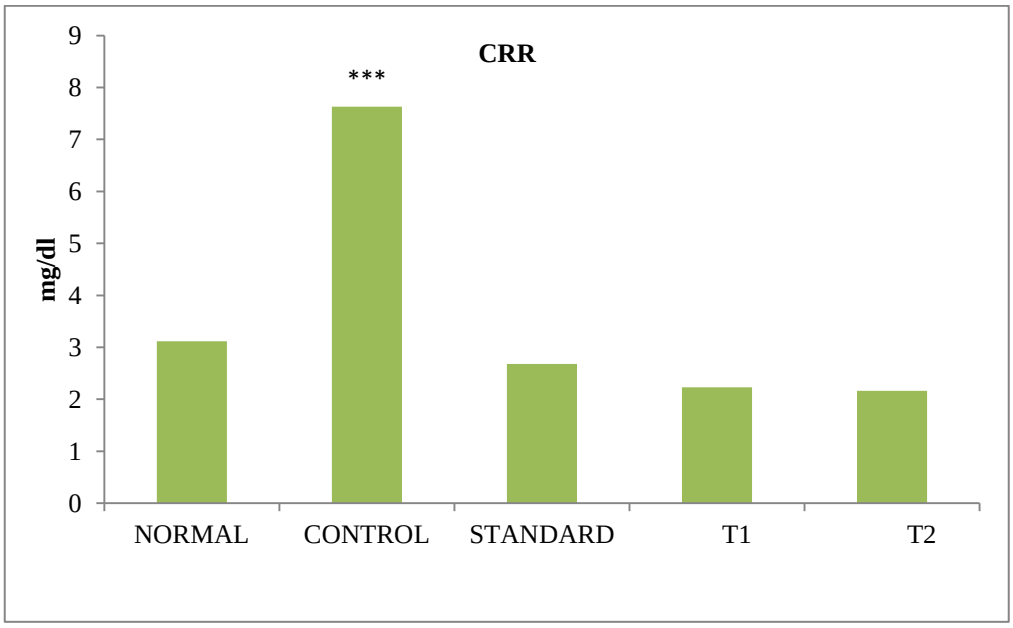


Graph 12 Histogram showing the effect of *Amaranthus* on Total Cholesterol of animals

N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control

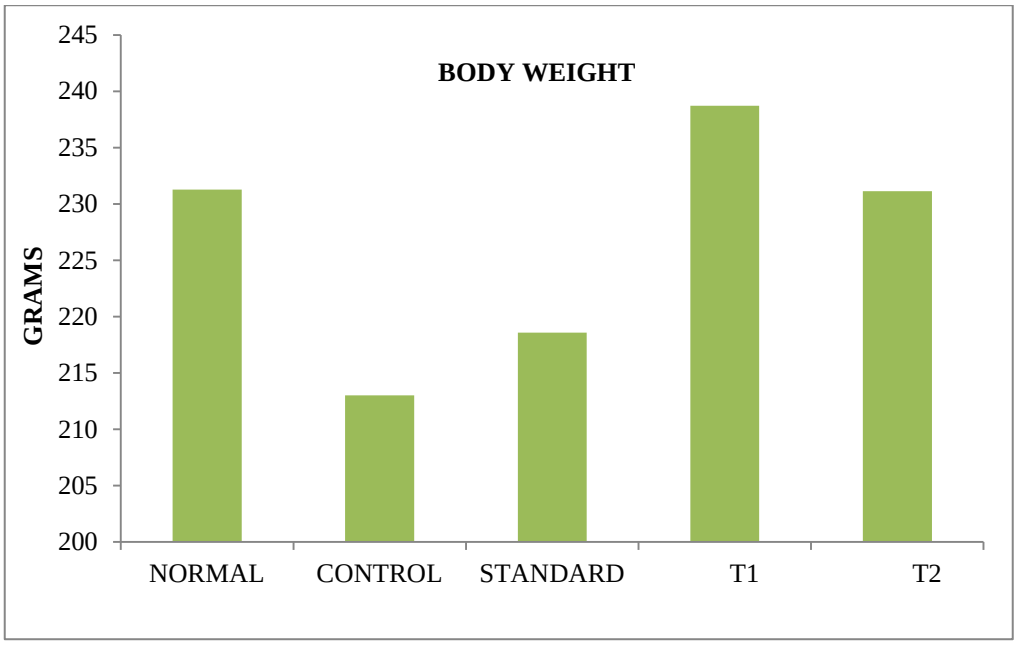


Graph 13 Histogram showing the effect of *Amaranthus* on Atherogenic Index of Animals

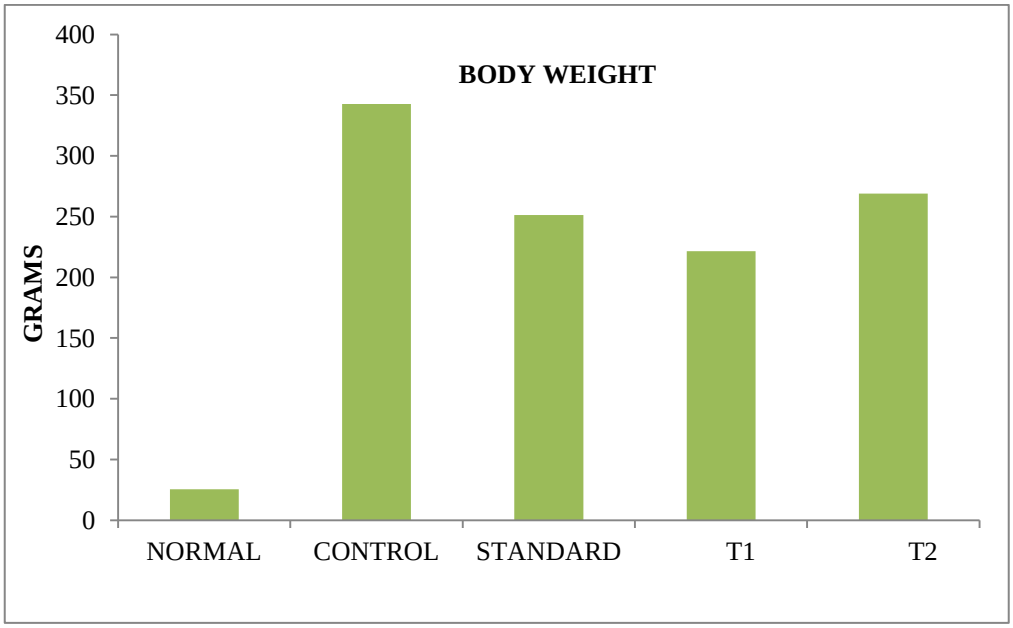


Graph 14 Histogram showing the effect of *Amaranthus* on Cardiac Risk Ratio of Animals

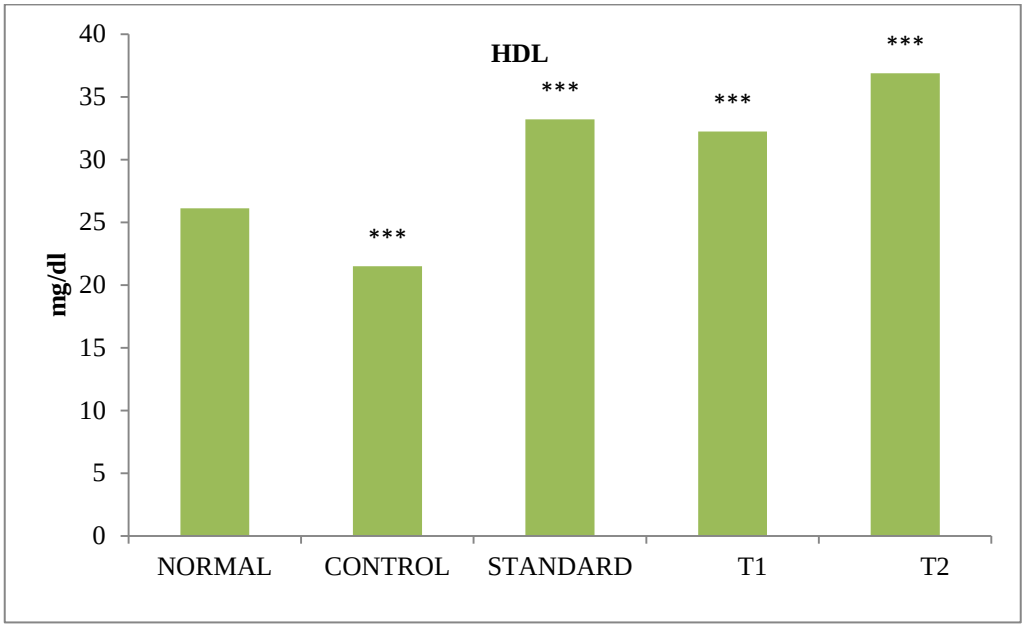
HIGH FAT DIET MODEL



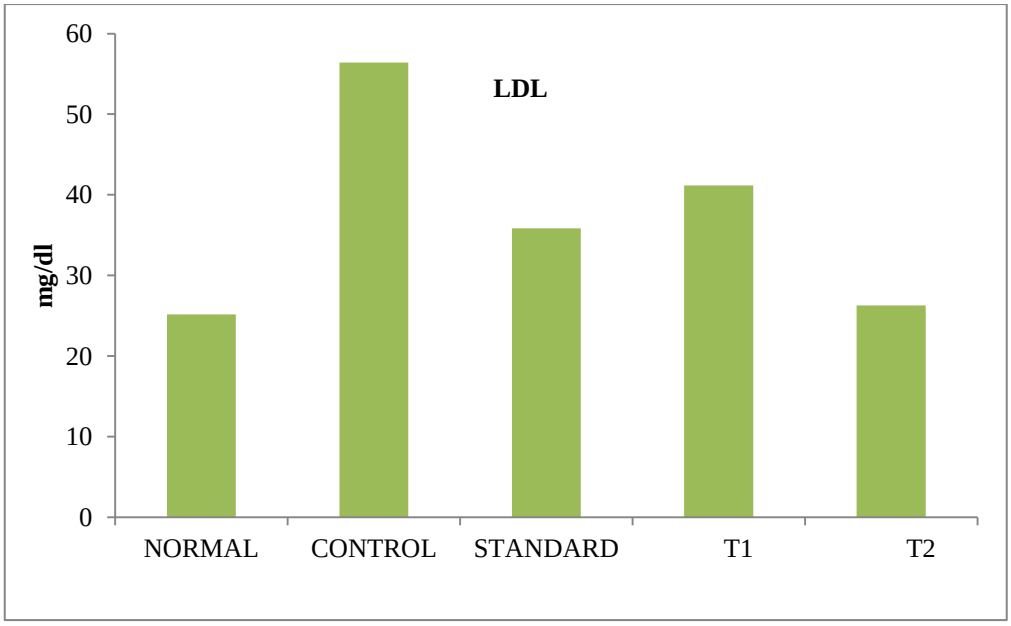
Graph 15 Histogram showing the Intial Body weight of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



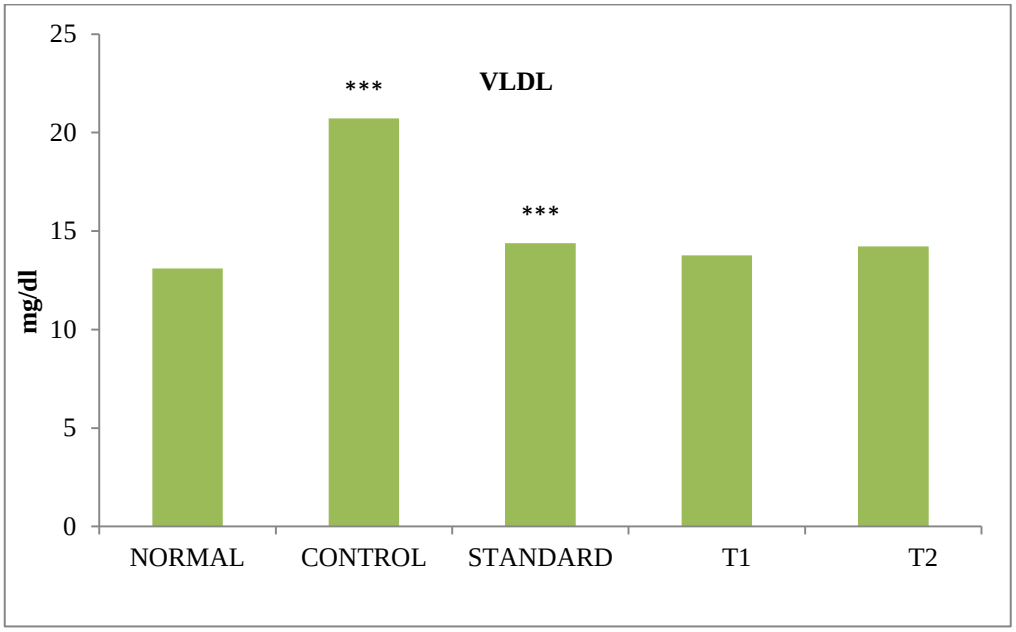
Graph 16 Histogram showing the effect of *Amaranthus* on Final Body weight of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



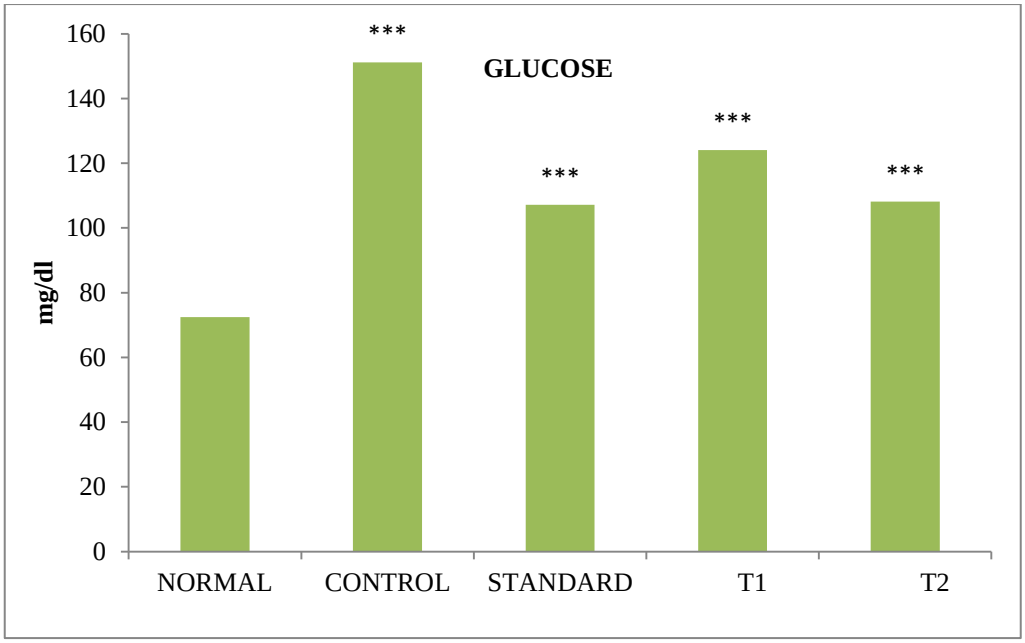
Graph 17 Histogram showing the effect of *Amaranthus* on HDL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



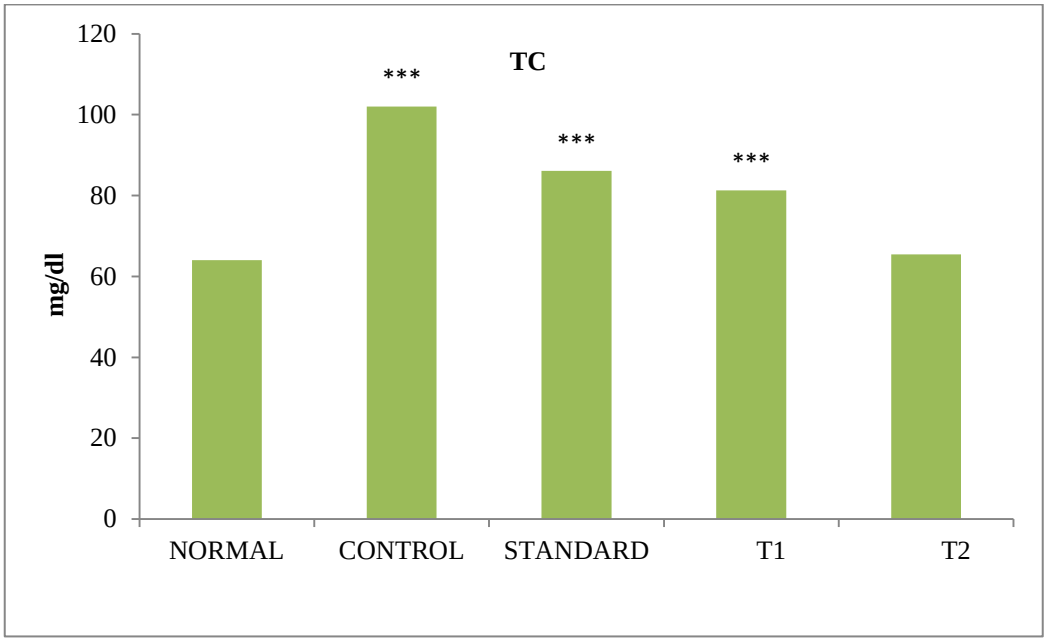
Graph 18 Histogram showing the effect of *Amaranthus* on LDL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



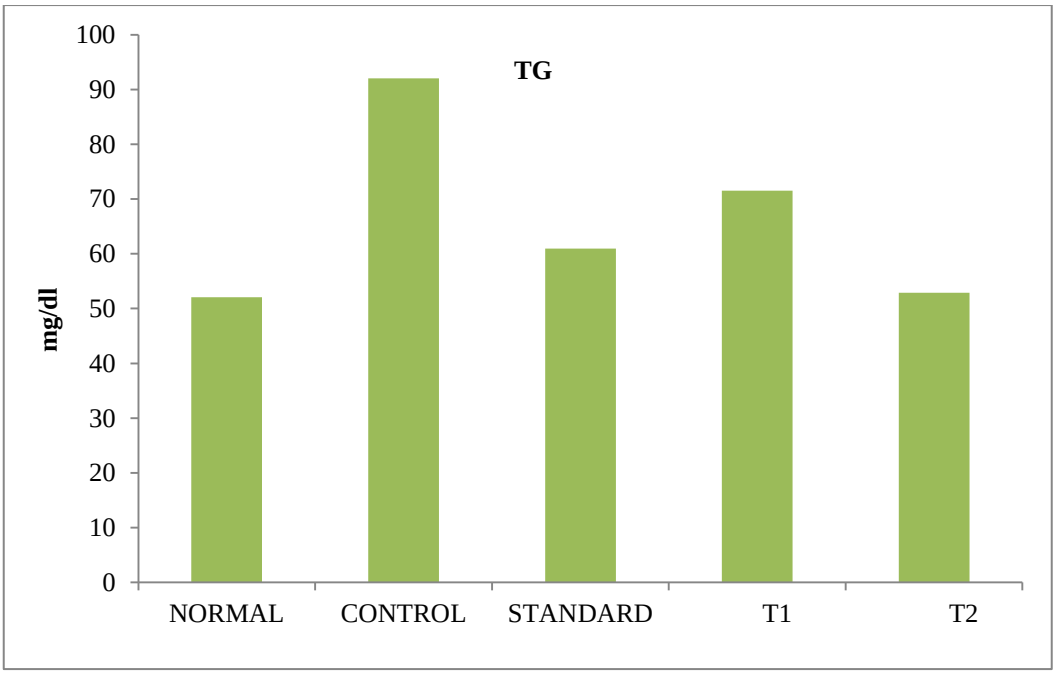
Graph 19 Histogram showing the effect of *Amaranthus* on VLDL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



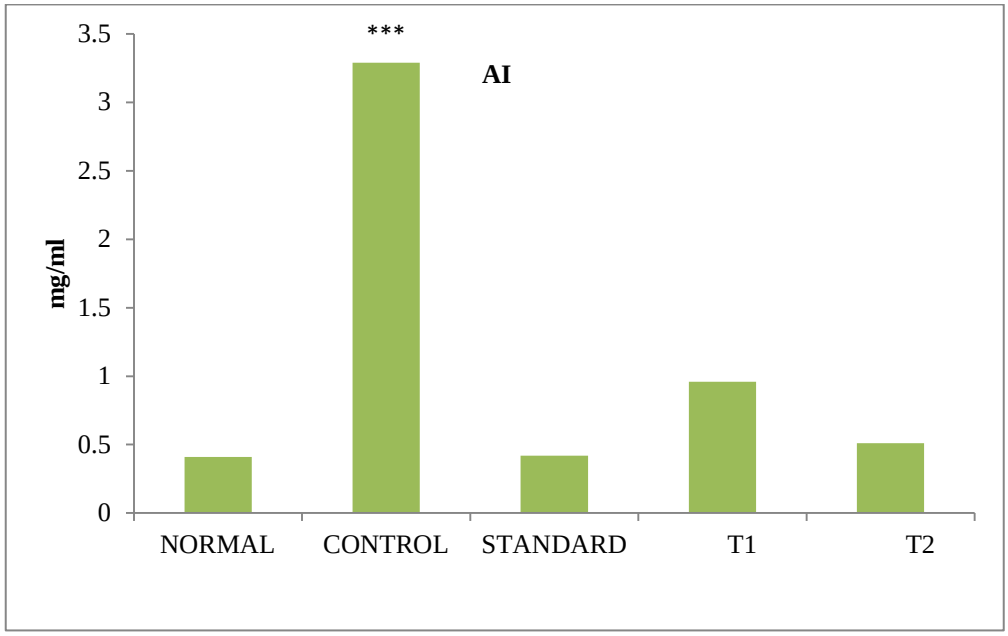
Graph 20 Histogram showing the effect of *Amaranthus* on GLUCOSE of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



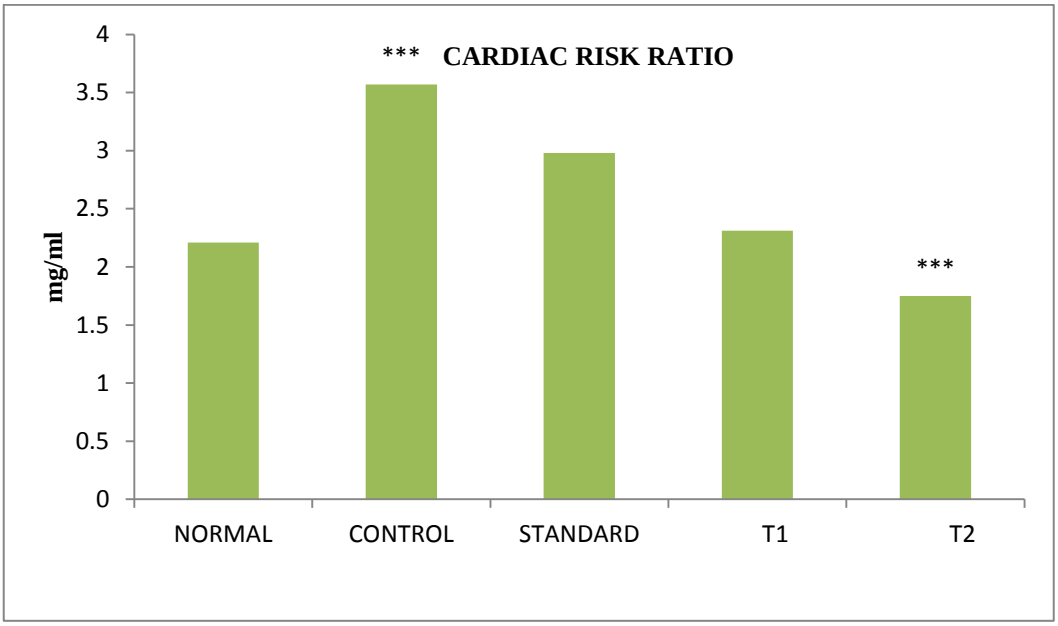
Graph 21 Histogram showing the effect of *Amaranthus* on TOTAL CHOLESEROL of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



Graph 22 Histogram showing the effect of *Amaranthus* on TRIGLYCERIDES of animals
N = 6; Significance: *** *P*<0.001, ** *P*<0.01, * *P*<0.05 from control



Graph 23 Histogram showing the effect of *Amaranthus* on Atherogenic Index of animals



Graph 24 Histogram showing the effect of *Amaranthus* on Cardiac Risk Ratio of animals

DISCUSSION

The result of this study showed that oral administration Methanol extract of *Amaranthus* leaf had a beneficial effect on the Anti-Hyperlipidemic. Phytochemical screening of methanol extract of the leaf and part of *Amaranthus* revealed the presence of flavonoids, alkaloids, tannins. Flavonoids have been shown to exert their antioxidant activity by various mechanisms by scavenging or quenching free radicals or by inhibiting enzymatic systems responsible for free radical generation [10-12]. Apart from being antioxidants, flavonoids have been reported to inhibit sodium-dependent vitamin C transporter 1 and glucose transport Isoform 2 (Glut 2), the intestinal transporter for vitamin C and glucose, leading to a decrease in the intestinal absorption of glucose, hence decrease in the blood glucose concentration [13]. Several researches have also demonstrated that

flavonoids act as reducer of hyperglycemia by causing inhibition of renal glucose reabsorption through inhibition of the sodium-glucose symporters located in the proximal renal convulated tubule [14-16]. Previous studies have reported some of these phytocomponents to elicit a wide range of biological activities which include hypolipidemia among others (Oladele et al., 1995). Specifically, saponin is known to elicit serum cholesterol lowering activity by causing resin-like action, thereby reducing the enterohepatic circulation of bile acids (Topping et al., 1980). In the process, the conversion of cholesterol to bile acid is enhanced in the liver resulting in concomitant hypocholesterolemia [17, 18].

Equally literature has reported the hypolipidemic effects of flavonoids, alkaloids and tannins [19]. The presence of these phytocomponentsin the extract in high concentrations could account for these observed biological effects, particularly hypolipidemic effects. The mechanism by which the extract exert the hypolipidemic effect may appear to be related to presence of flavonoid among other secondary metabolites or bioactive chemical constituents found in the plant extract which may be an active constituents in a group or an individual responsible for the hypolipidemic activity of the plant extract [19]. The plant extract of *Amaranthus* didn't show any mortality and toxicity even at highest dose of 2000mg/kg body weight employed. Hence, present research study was carried out using dose 400mg/kg body weight. [17-19]. The presence of the steroids reduces the absorption of cholesterol and decreases the cholesterol concentration. Secondary metabolite like the flavonoids, saponins, reduces the cholesterol levels. Saponins will act as anti hyperlipidaemics by binding with the cholesterol and is readily absorbed by the bile acids causing the reduction in extra hepatic circulation and increases the metabolism of cholesterol to sterols through the fecal excretion. Saponins will as reported to increase the lipoprotein lipase activity and helps in the faster removal of free fatty acids from circulation causes decrease in fatal cholesterol.

Elevated cholesterol levels will promotes the atherosclerosis. High cholesterol levels are associated with the increased incidence of coronary heart diseases. Reduction in the cholesterol and the HDL concentration significantly reduces the cholesterol levels. Atorvastatin is a member of the drug class of statins, it is the first specific inhibitor used for lowering cholesterol (hypo-lipidemic agent) in those with hyper-cholesterolemia and so preventing cardio vascular disease. It is a naturally occuring drug found in food such as oyster mushrooms and red yeast rice. It reduces the levels of "bad" cholesterol (LDL) and Triglycerides in the blood, while increasing levels of "good" cholesterol (HDL). It is an inhibitor of 3-hydroxy-3 methyl glutaryl-CoA reductase (HMG-CoA reductase), an enzyme that catalyses the conversion of HMG-CoA to mevalonate. Mevalonate is a required building block for cholesterol biosynthesis and Atorvastatin interferes with its production by acting as a reversible competitive inhibitor foe HMG-CoA, which binds to the HMG-CoA reductase. It works by slowing the production of cholesterol in the body. Buildup of cholesterol and fats along the walls of the blood vessels (A process known as Atherosclerosis) decreases blood flow and therefore, the oxygen supply to the heart, brain and other parts of the body. Lowering blood levels of cholesterol and fats may help to decrease the risk of heart disease, Angina (chest pain), strokes and Heart attacks. In addition to taking a cholesterol-lowering medication, making certain changes in our daily habits can also lower the blood cholesterol levels.

Effect of different extracts of *Amaranthus*on serum lipid profile and Atherogenic Index, % protection

The serum level of triglycerides and cholesterol and it can be seen that the HFD group and Triton-x-100 shows significant hyperlipidemia when compared with the normal control group. The extract treated groups and the standard treated group significantly decreased the serum levels of cholesterol and triglycerides when compared with the HFD control group and Triton-x-100 ($p<0.05$). The effect of ethanol extract on serum lipid levels was as better that of the standard treated group, showing the hypolipidemic potential of the plant. An increase of HDL-cholesterol level was also observed. Decrease in glucose levels are observed in methanolic extract compared to HFD control group ($p<0.001$). Both 200 and 400 mg/kg body wt. 0.obtusata treated animals and 10 mg/kg body wt of Atorvastain treated animals in both models showed decrease in the atherogenic index and increased percentage of protection.

Effect of different extracts of *Amaranthus* on Total protein profile

The serum level of total protein and it can be seen that the Triton-x-100 group shows significant decrease in total protein levels when compared with the normal control group. The extract treated groups and the standard treated group significantly increased the serum levels of total protein when compared with the Triton-x-100 control group ($p<0.001$). The effect of methanol extract on levels was better as that of the standard treated group, showing the hypolipidemic potential of the plant.

Effect of different extracts of *Amaranthus* on SGOT, SGPT and ALP levels

AST, ALT, SGOT, SGPT, and GGT and Alkaline Phosphatase are abbreviations for proteins called enzymes which help all the chemical activities within cells to take place. Injury to cells releases these enzymes into the blood. They are found in muscles, the liver and heart. Damage from alcohol and a number of diseases are reflected in high values. AST/SGOT, ALT/ SGPT are also liver and muscle enzymes. They may be elevated from liver problems, hepatitis, excess alcohol ingestion, muscle injury and recent heart attack. An atherogenic diet has been reported to induce glomerulosclerosis/nephropathy and mild tubular and hepatic damage experimental rats [101] In case of the effect of methanol extract on enzymes (SGOT, SGPT and ALP), the extract shows significantly lower levels of SGOT, SGPT and ALP in comparison to Triton-x-100 control group ($p<0.05$). Here the maximum reduction was observed for standard followed by methanolic extract. Therefore, it can be confirmed that, in present investigation significant Anti-Hyperlipidemic potential of Amaranthus shrub may be due to flavonoids, alkaloids, tannins content, which were confirmed by preliminary phytochemical screening.

CONCLUSION

Phytochemical screening of the extract shows the presence of chemical constituents like Alkaloids, steroids, fixed oils, cardio tonic aglycones, flavonoids, saponins, carbohydrates, proteins, resins. Acute toxicity tests were performed according to the OECD guide line no.423, LD50 value was found to be 200mg/kg and 400mg/kg. Anti Hyperlipidaemic activity was performed by using the high fat diet and Triton-x-100 induced method. In the present study an increase in plasma HDL-cholesterol with a concomitant percentage decrease from other lipid was observed. It can be concluded from the present data that the levels of total serum cholesterol, triglyceride and MDA which are actually raised in high fat diet, can be lowered significantly with *Amaranthus* And total proteins which is actually lowered in Triton-x-100 can be raised significantly with *Amaranthus***.** Atherogenic index which actually raised in atherogenic diet and Triton-x-100, can be lowered significantly with *Amaranthus* and a very good % protection was seen with *Amaranthus* and standard drug. The extract also show increase in the glucose tolerance of the rats and decrease in the fasting blood glucose level of diabetic rats, showing the hypoglycaemic activity of the plant which is most pronounced in methanol extract. In nutshell the extract of *Amaranthus* possesses significant hypoglycaemic activity and anti Hyperlipidaemic activity, which is the first claim in this respect.

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