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Hypocholestrolemic potential of seed extracts of Artocarpus Hirsutus: An In Vivo study

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ABSTRACT

The genus Artocarpus belongs to the family Moracea which comprises of about 60 genera and over 1000 species. Artocarpus species are known for its edible fruit with high nutritive values. *Artocarpus hirsutus* Lam. is one among the five available varieties of jackfruits. The aim of the present study is to evaluate hypocholesterolemic effect on roasted and non roasted seeds of Artocarpus hirsutus. The current study was designed to examine the cholesterol lowering activity of *A. hirsutus* seed extracts in hyperlipidemic rat model induced with 25% fat rich diet and details of parameters associated with hyperlipidemia (Cholesterol, Triglycerides, HDL & LDL and serum marker enzymes) were assessed. Treatment of hypercholesterolemic rats with *A. hirsutus* seed extracts induced marked significant decrease of serum total cholesterol, triglycerides and LDL-cholesterol concentrations as compared to the hypercholesterolemic rats.

Keywords: Artocarpus Hirsutus, Hypocholesterolemic.

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INTRODUCTION

Hypercholesterolemia is a secondary metabolic dysregulation associated with diabetes. Besides the cause effect relationship with diabetes, elevated serum level of triglycerides, cholesterol and LDL are major risk factors for the premature development of cardiovascular disease like arthrosclerosis, hypertension, coronary heart disease etc. (Mani *et al* 2012, Parasuraman *et al* 2010). Increased plasma lipid levels mainly total cholesterol, triglycerides and LDL along with decrease in HDL are known to cause hyperlipidemia which is the reason for initiation and progression of atherosclerosis impasse (Sikarwar *et al* 2012). Antihyperlipidemic agents having various pharmacological actions are being tested clinically. Elevated lipid levels result from increased absorption through the gut or enhanced endogenous synthesis and therefore two ways are feasible to reduce hyperlipidemia; to block endogenous synthesis or to decrease absorption.

Wild Jackfruit, also called Wild Jack is having the Latin name *Artocarpus hirsutus Lam*. Belonging to the Moraceae family. It is common in Western Ghats form north Karnataka to Malabar Coast and Travancore[1]. *Artocarpus hirsutus* is a tropical evergreen tree species that is native to India, primarily in Kerala. It grows at an altitude ranging from sea level at an elevation of 1000 meters in places with an annual rainfall of 1500 mm or more[2]. Artocarpus hirsutus is an evergreen tree with a dense crown growing up to 50 metres tall. The straight, cylindrical bole can be 150cm or more in diameter. The heartwood is yellowish-brown; the sapwood white. The wood is moderately hard, durable; it lasts well in water and is not attacked by white ants. Fruits are edible, bright yellow, ovoid covered with spines, seeds ovoid and white. It required warm humid climate heavy rainfall and thrives week in any type of soil. Kerala's own fruit locally called 'Anjili Chakka' (Artocarpus hirsutus) .

Vernacular Names of *Artocarpus hirsutus*

English – Wild Jack

Kannada- *Hebbalasu, hebbe-lasu*

Malayalam- *Ayani, Anjili , Ayaniplavu, Annali, Annili, Aini, Ayari*

Marathi- Pat-*phanas, Ranphanas*

Tamil- *Kattuppala. Akkini,Anjili*

Telagu- *Pejuta*

Figure 1: Fruits of Artocarpus hirsutus

The plant A. Hirsutus is notable for its valuable medicinal properties. Bark has the properties to cure ulcers, diarrhea and pimples. Roasted seeds powder mixed with honey is used for the treatment of asthma. Oil from the fruits are used for the treatment of skin diseases. Grinded bark of *Artocarpus hirsutus lam* is a constituent of many herbal medicines for piles, and Grinded bark is smeared on the affected part to cure piles. Latex of *Artocarpus hirsute is used* for asthma and seeds are use as appetizer. Burnt leaves ash is taken internally to treat abdominal problems. Dry leaves are useful in treating buboes and hydrocele. Fruits are rich source of carbohydrates, ß-carotene and essential amino acids. Unripe fruits are useful in vitiated conditions of *vata* and *pitta* and anorexia. The ripe fruits posses sour, sweet, cooling, appetizing, constipating and aphrodisiac properties. It causes flatulence, colic, tridosa and rakta vitiations. Studies on pylorus ligated rats demonstrates that the *A. hirsutus* stem bark extract reduces the gastric secretary volume, acidity and ulceration[3] An infusion of the bark is applied to cure small pimples and cracks on the skin, and the powdered bark is used to heal sores[4]. Bark ash mixed with coconut oil is used externally against 'dhobi's itch' and ringworm. Bark paste in coconut oil can be applied for snake bite[5]. Roots and bark decoctions are used to cure diarrhoea whereas leaves used along with white camphor and root of curcuma to treat venereal bubones and chronic haemorrhage. Juice of cooked fruits is potential for inducing appetite and applied to the anus to relieve the pains of haemorrhage**.** It's barks are used to cure diarrhea, pimples and ulcers[6].Grinded bark of *Artocarpus hirsutus* is a constituent of the medicine for piles, and Grinded bark is smeared on the affected part to cure piles[7.] The timber of the plant is used for house and boat building and furniture manufacture.

MATERIALS AND METHOD

Collection of Samples

Fruits of *Artocarpus hirsutus* Lam. were collected from Mannarkkad area of Palakkad district, Kerala. Healthy plants with previous history of giving fruits were selected and identified. The fruits and seeds were authenticated by Dr. Usman Arerath, Young Scientist (SERB-DST), Department of Botany, MES Kalladi College, Mannarkkad, Palakkad, Kerala. Botanical characters were also compared with various floras.

Preparation of Seed Extract

Seeds were taken out from the fruit, washed properly and sun dried for further evaluation and studies. Half the seeds were roasted and half were non roasted and taken separately for further studies. The roasted and non roasted seeds were powdered separately. Then both will extracted separately by Hydroalcoholic and Hexane.

Preparation of plant extract for dosing:

The hexane and hydroalcoholic extracts were dissolved in water. The plant extracts used for the study were suspended each time with water for injection.

Experimental Animals

Animal species: Rats

Strain: Wister albino rats

No: of animals and sex: 30 male rats.

Body weight range: 175-295g.

Age at treatment: 8 to 12 Weeks

Conditions:

Animals were housed under standard laboratory conditions: air- conditioned environment with adequate fresh air supply with IVC system (Air changes 15 per hour), room temperature 21.0 to 24.0°C, relative humidity 57-65%, with 12 hours light and 12 hours dark cycle. The temperature and relative humidity were recorded daily.

Housing:

Single animal was housed in a standard polysulphonate cage(Size: L 300 x B 170 x H 140 mm) with stainless steel top grill mesh having facilities for holding pelleted food and drinking water in water bottle fitted with stainless steel sipper tube. Sterilized paddy husk was provided as bedding material.

Acclimatization:

The animals were acclimatized for a minimum period of seven days to laboratory conditions and were observed for clinical signs daily. Veterinary examination of all the animals was recorded on the day of receipt and on 7^{th} day of acclimatization.

Diet:

The animals were fed *ad libitum* throughout the acclimatization and study period. Normal and High Fat Laboratory animal feed (Manufactured by VRK Nutritional Solutions, Maharashtra) was provided.

Water:

Water was provided *ad libitum* throughout the acclimatization and study period. Deep bore-well water passed through activated charcoal filter and exposed to ultraviolet rays in Aqua guard water filter cum purifier (Manufactured by Eureka Forbes Ltd., Mumbai) was provided in plastic water bottleswith stainless steel sipper tub Study Design

The objective of this study was to assess the potential of *A. hirsutus* seed extract to alleviate high fat diet induced hypercholesterolemia in laboratory rats. Male Wistar Albino rats were utilized in this study. The rats were fed with pellet diet *ad libitium* and were acclimatized to laboratory conditions for 7 days prior to theexperiment.

Rats were divided into five groups and were fed with two dietary regimes either Normal Pellet Diet (for normal control group) or High Fat Diet (HFD) containing 24.7% fat and 18.0% protein (for all groups except normal control group). Hypercholesterolemia was induced in high fat control group and all treatment group animals using HFD and all animals received treatment in the following manner.

Group No.	Group	Treatment for 28 days
Group-I	Vehicle Control	Normal diet + Distilled water -1ml/100g body weight, per oral (6 nos.)
Group-II	High Fat Diet Control	High Fat Diet (HFD) + Distilled water -1ml/100g body weight, per oral (4 nos.)
Group-III	Low dose	HFD +*A. hirsutus* extract A - 150mg/kg bodyweight, per oral (2 nos.)
		HFD +*A. hirsutus* extract B - 150mg/kg bodyweight, per oral (2 nos.)
		HFD +*A. hirsutus* extract C - 150mg/kg bodyweight, per oral (2 nos.)
		HFD +*A. hirsutus* extract D - 150mg/kg bodyweight, per oral (2 nos.)
Group-IV	High Dose	HFD + *A. hirsutus* extract A - 300mg/kg body weight, per oral (2 nos.)
		HFD + *A. hirsutus* extract B - 300mg/kg body weight, per oral (2 nos.)
		HFD + *A. hirsutus* extract C - 300mg/kg body weight, per oral (2 nos.)
		HFD + *A. hirsutus* extract D - 300mg/kg body weight, per oral (2 nos.)
Group-V	Standard	HFD + Atorvastatin (10mg/kg body weight) peroral (4 nos.)

After completion of treatments, all animals were fasted overnight and were euthanized on next day by overdose of Thiopental sodium injection (i/p). Blood samples were collected immediately, by cardiac puncture and allowed to clot for 30 min at room temperature. Serum separated by centrifugation and used for the estimation of biochemical parameters like lipid profile, AST, ALT and ALP. The liver was collected immediately followed by fixation in 10% (w/v) buffered formalinand used for histological studies.

Administration of Test Item

The test item Artocarpus hirsutus extract was administered through oral route by gavageto the animal after formulation preparation using rat gavaging needle fitted to graduated syringe. The administration of the test item was done after calculating the dose for each respective group and formulation was made with the dose concentration as mentioned in the study design. This procedure of administration was followed for 28 consecutive days.

Observation parameters

Following parameters were observed during the study.

1. Body weight and liver weight measurements: The body weight of each rat was recorded prior to treatment on Day 1, weekly thereafter and at terminal sacrifice of the study and group mean body weights were calculated. Liver weight of each rat was noted at the time of sacrifice, and relative weight of liver was determined.
2. Serum Biochemistry: At the end of treatment (on 28th day) all treatment group animals were fasted overnight. Ad libitum water was given during fasting and were euthanized on next day by overdose of Thiopental sodium injection (i/p). Blood samples were collected immediately, by cardiac puncture and allowed to clot for 30 min at room temperature. Serum separated by centrifugation was used for determining the following clinical chemistry parameters;
3. Serum lipid profile: Serum liver function enzymes:
    - Total Cholesterol (TC)
    - Aspartate aminotransferase (AST)
    - Triglycerides (TG)
    - Alanine aminotransferase (ALT)
    - HDL- Cholesterol
    - Alkaline Phosphatase (ALP)
    - LDL -Cholesterol
4. Tissue collection: Liver was collected from the euthanized animals and preserved in 10% neutral buffered formalin. The tissues were embedded in paraffin wax, sectioned at five µm and stained with haematoxylin and eosin.
5. Histopathological Examination: Detailed histopathological examination was performed on the pancreatic tissues of all animals from the control and the dosage groups, sacrificed at scheduled termination.
6. Data Compilation: All the observations made during the study period were recorded and

tabulated.

7. Statistical Analysis: The data on body weight, clinical chemistry parameters and hormone levels, generated from the present study were subjected to computer statistical analysis using GraphPad Prism software, Version 5.00, USA. 2007.

One way ANOVA with Dunnets post-test was done for different treatment groups comparing with the diabetic control group data. All analysis and comparisons was evaluated at 5%significance level.

RESULTS AND DISCUSSION

Determination of hypocholesterolemic potential of Artocarpus Hirsutus seed extract in Wistar rats.

Body weight changes and liver weight measurements

HFD control rats showed marked increase in body weight during treatment period compared to normal control rats, but was not found to be statistically significant. At 4 weeks after treatment, average body weight of normal control and HFD (Group 2) rats were 295.83 ± 7.46 and 346.250 ± 17.002g, respectively. Similarly, treatment with seed extracts of *Artocarpus hirsutus* in HFD fed rats did not show any significant difference in body weight compared to normal control animals. At 4 weeks after the treatment, average body weight of *A. hirsutus* seed extract (150mg/kg bwt.), *A.hirsutus* seed extract (300mg/kg bwt.) and Atorvastatin (standard drug) groups were 300.625 ± 11.078, 304.375 ± 12.227, and 320.000 ± 17.440 g, respectively.

During 2nd week of treatment there was significant elevation in the body weight gain percentage of HFD control rats (12.393%, $p<0.001$), *A. hirsutus* seed extract (low and high dose) treated rats (11.746% and 12.190% respectively, $p<0.001$) and Atorvastatin treated rats (10.648%, $p<0.001$), when compared to normal control rats (3.476%). However, during subsequent weeks there observed no significant difference in percent body weight gain among different treatment groups compared to normal and HFD control groups.

On sacrifice significant increase in liver weight was noted in HFD control rats (11.37 ± 0.82, $p<0.001$) compared to normal rats (7.78 ± 0.142). However, treatment with *A. hirsutus* seed extract**,** at 300mg/kg bwt., effected significant reduction in rat liver weight (7.97 ± 0.338) compared to HFD control animals. *A. hirsutus* seed extract (150mg/kg bwt.) and Atorvastatin treated animals also showed marked decrease in absolute weight of liver and was comparable with that of normal control rats. Relative weight of liver was found to be elevated in HFD control rats (3.308 ± 0.207, $p<0.01$) compared to normal rats (2.62 ± 0.054). However, treatment with *A.*

hirsutus seed extract (300mg/kg bwt.) resulted in statistically significant difference in relative liver weights of rats from HFD control animals.

Refer Table-1, 2 & 3 Figures -1, 2 & 3 and Appendix-1

Table 1: **Summary of bodyweight (g) during treatment periods**

Groups		Day1	Week			
			1	2	3	4
Group- I (Normal Control)		243.333±7.149	270.00±6.708	279.167±5.974	288.333±7.149	297.500±6.677
Group- II (HFD Control)		212.500±8.292	272.500±15.612	306.250±17.722	327.500±18.085	346.250±17.002
Group- III (Low dose)	A	190.000±10.000	230.000±5.000	255.000±0.000	272.500±2.500	277.500±7.500
	B	207.500±7.500	237.500±7.500	265.000±10.000	282.500±7.500	290.000±5.000
	C	220.000±0.00	272.500±22.500	302.500±22.500	322.500±17.500	340.000±15.000
	D	225.000±20.000	242.500±22.500	275.000±25.000	287.500±27.500	295.000±30.000
Group- IV (High dose)	A	192.500±7.500	242.500±7.500	277.500±12.500	292.500±22.500	300.000±25.000
	B	210.000±5.000	260.000±10.000	295.000±15.000	312.500±12.500	317.500±12.500
	C	207.500±12.500	247.500±22.500	275.000±25.000	285.000±25.000	295.000±25.000
	D	237.500±57.500	265.000±55.000	290.000±55.000	297.500±47.500	305.000±50.000
Group- V(Standard)		208.750±8.509	258.750±7.465	286.250±7.739	305.000±11.365	320.000±17.440

Values are expressed as mean ± SEM

Table 2: **Summary of body weight gain (%) during treatment**

Groups		Body weight gain (%)		
		2^{nd} week	3^{rd} week	4^{th} week
Group- I(Normal Control)		2.777±1.230***	2.031± 0.914*	2.598± 0.736
Group- II(HFD Control)		12.393± 0.991	6.986± 0.448	5.842± 1.245
Group- III (Low dose)	A	10.922±2.411	6.863±0.980	1.818±1.818
	B	11.557±0688	6.649±1.194	2.680±0.956
	C	11.085±0.915	6.772±2.157	5.485±1.073
	D	13.422±0.214	4.500±0.500	2.548±0.626
Group- IV (High dose)	A	14.383±1.617	5.254±3.367	2.513±0.661
	B	13.407±1.407	5.991±1.152	1.603±0.064
	C	11.111±0.00	3.667±0.333	3.536±0.310
	D	9.859±2.046	3.191±3.191	2.449±0.449
Group- V(Standard)		10.648± 0.590	6.469± 1.352	4.719± 1.979

Values are expressed as mean ± SEM

*** P<0.001 when compared with Group II

Table 3: **Summary of Absolute and Relative Liver weights**

Groups		Absolute liverweight(g)	Relative liverweight (g/100g)
Group- I(Control)		7.785±0.142***	2.621± 0.054**
Group- II(HFD Control)		11.370± 0.382	3.308± 0.207
Group- III(Low dose)	A	9.035±0.265	3.256±0.008
	B	8.770±0.120	3.024±0.011
	C	11.015±1.345	3.229±0.253
	D	8.825±0.965	2.989±0.023

Group- IV(High dose)	A	7.720±0.610**	2.574±0.011*
	B	8.865±0.665	2.788±0.100
	C	7.230±0.610**	2.451±0.001**
	D	8.065±0.765*	2.675±0.188
Group- V(Standard)		9.265± 0.969	2.881± 0.194

Values are expressed as mean ± SEM

* P<0.05, ** P<0.01, *** P<0.001 when compared with Group II

Serum lipid profile

In the present study, there was a significant elevation in the Total Cholesterol (TC), Triglyceride (TG) and Low Density Lipoprotein (LDL) levels in high fat diet induced hypercholesterolemic (HFD control) rats (125.875 ± 2.481, 116.650 ± 11.919 and 53.395 ± 3.696 respectively) compared to normal diet fed rats (66.267 ± 3.914, 63.133 ± 6.588 and 1.523 ± 0.804 respectively). The treatment with *A.hirsutus* seed extract and atorvastatin significantly decreased the levels of TC, TG and LDL compared to HFD control rats; specifically treatment with *A.hirsutus* seed extract A (300mg/kg bwt.) resulted in significant reduction in TC and TG levels in high fat diet fed rats (47.550 ± 6.450 and 46.650 ± 3.750 respectively). However, there was no significant difference in the level of HDL among different groups when compared to the values of the normal control rats. Refer Table-4, Figure -4 and Appendix-2.

Table 4: **Summary of Serum Lipid Profile**

Groups		**TC(mg/dl)**	**TG(mg/dl)**	**HDL(mg/dl)**	**LDL(mg/dl)**
Group- I(Control)		66.267± 3.914**	63.133± 6.588**	52.117± 3.669	1.523±0.804***
Group- II(HFD Control)		125.875± 2.481	116.650±11.919	49.150± 3.946	53.395± 3.696
Group- III(Low dose)	A	88.200±17.100	91.000±4.100	67.000±15.600	3.000±2.320***
	B	53.900±2.200**	65.900±12.000	40.200±4.600	0.520±0.00***
	C	57.300±2.300**	100.250±7.250	36.650±3.550	0.600±0.200***
	D	95.900±47.000	115.350±20.750	66.900±32.000	5.930±10.850***
Group- IV	A	47.550±6.450**	46.650±3.750*	35.700±4.900	2.520±2.300***
(High dose)	B	65.500±3.700*	73.950±14.950	49.050±2.250	1.660±1.540***
	C	70.250±12.650*	81.150±9.150	52.900±9.900	1.120±4.580***
	D	80.350±21.050	66.450±7.250	48.150±17.750	18.910±1.850***
Group- V(Standard)		62.350± 8.155**	58.575± 18.219**	47.800± 6.781	2.835±1.925***

Values are expressed as mean ± SEM

* P<0.05, ** P<0.01, *** P<0.001 when compared with Group II

Serum Liver function enzymes

HFD control rats showed a significant increase in the serum biomarker enzymes, AST, ALT and ALP (p<0.05) when compared to the values of normal control rats. Oral administration of atorvastatin significantly decreased the serum levels of AST and ALT. Treatment with *A.hirsutus* seed extract A (300mg/kg bwt.) effected significant reduction in ALT levels when compared to

HFD control rats. However, AST levels were not much reduced among *A. hirsutus* seed extract treated animals. Also there was no significant difference in the level of ALP among different groups when compared to the values of the HFD control group.

Refer Table-5, Figures -5 and Appendix-3

Table 5: **Summary of Serum Liver Function Enzymes**

Groups		AST(U/L)	ALT(U/L)	ALP(U/L)
Group- I(Control)		94.867± 8.714*	34.900± 2.741*	242.583± 15.256*
Group- II(HFD Control)		154.600± 7.201	57.900± 3.545	352.72± 15.013
Group- III(Low dose)	A	87.100±4.500	37.700±5.800	365.650±29.450
	B	108.950±27.850	30.150±1.650*	258.050±1.550
	C	125.500±16.400	34.500±4.300	236.400±4.700
	D	124.000±46.100	44.450±15.450	282.750±71.350
Group- IV(High dose)	A	98.500±2.800	24.000±0.300**	243.600±19.000
	B	102.450±13.750	32.800±3.700	266.300±25.100
	C	129.600±48.400	36.150±9.850	325.200±52.500
	D	111.250±23.850	55.450±13.450	285.150±76.650
Group- V(Standard)		83.375± 5.259*	31.300± 4.868**	285.87± 34.045

Values are expressed as mean ± SEM

* P<0.05, ** P<0.01, *** P<0.001 when compared with Group II

Gross and Histopathological evaluation

On gross examination, moderate fatty change was noted in the liver of HFD control rats; however, all normal control group rats and most of the treatment group animals showed almost normal appearance of liver. Histological examinations of the rat liver tissue sections with (H & E) stain under light microscope were conducted. Liver tissue of normal control rats, showed normal architecture with radiating appearance of hepatic chords. In HFD control rats, the normal structure of liver was lost and most hepatocytes contained numerous fat vacuoles within cytoplasm (fatty infiltration). Central vein and portal triad were dilated; Sinusoidal spaces appear compressed In most of the rats treated with *A. hirsutus* seed extracts and standard Atorvastatin, normal architecture of hepatic tissue was almost regained; there was marked reduction or almost absence of fat vacuoles within the hepatocytes in most of the treatment groups.

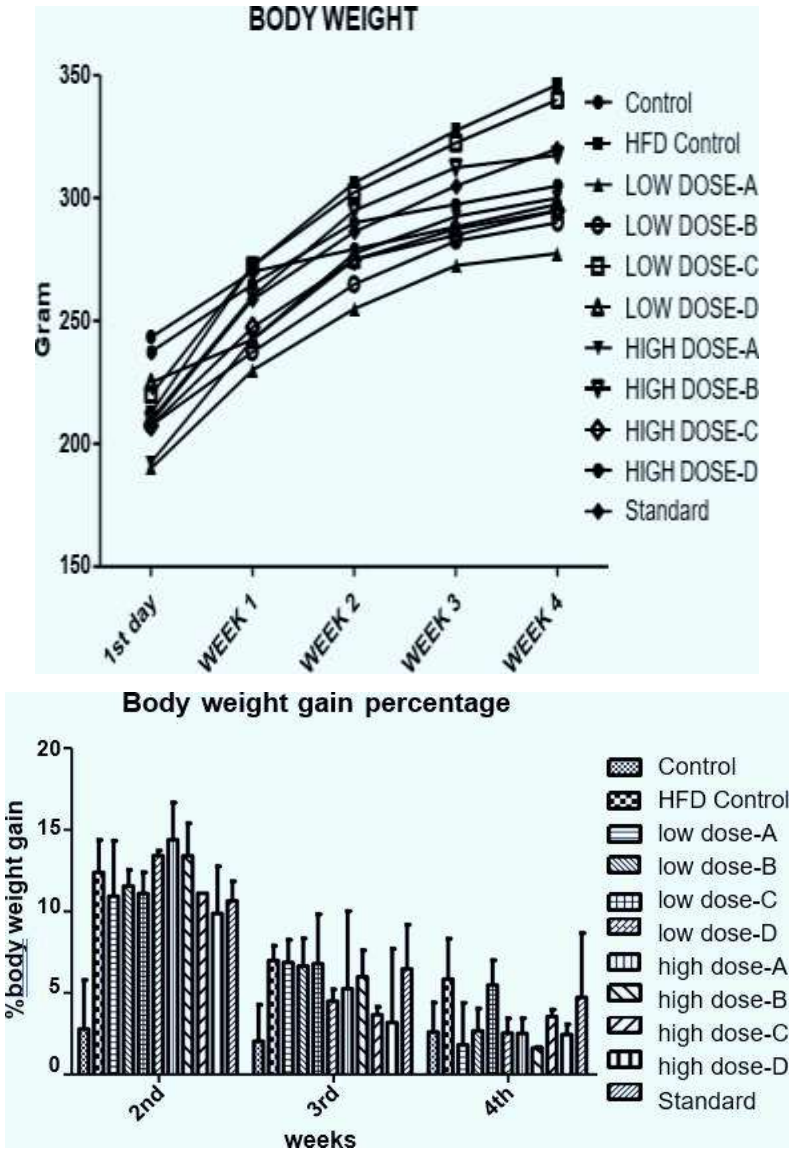


Figure 2: Effect of Artocarpus hirsutus on Body Weight

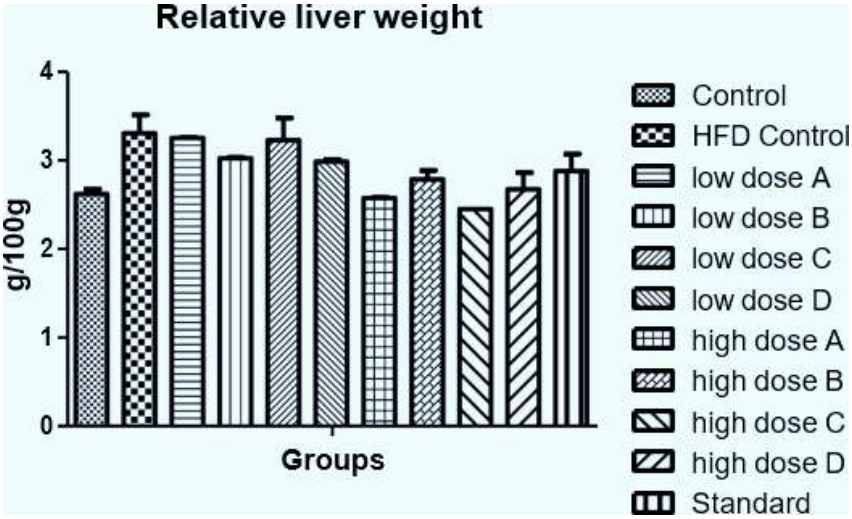


Figure 3: Effect of Artocarpus hirsutus on Relative Liver Weight (g/100g)

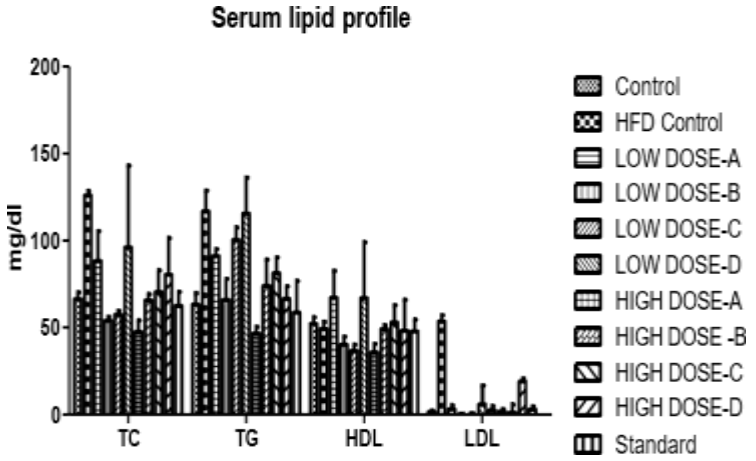


Figure 4: Effect of Artocarpus hirsutus deed extract on Serum Lipid Profile

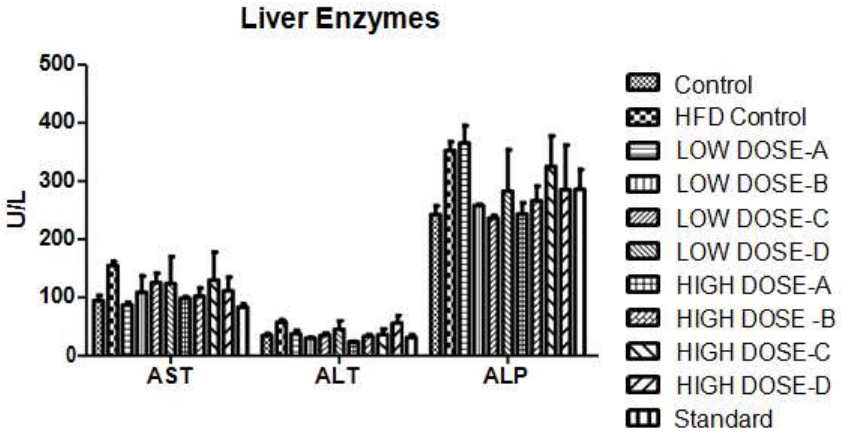


Figure 5: Effect of Artocarpus hirsutus seed extract on Serum Liver Function Enzyme Levels

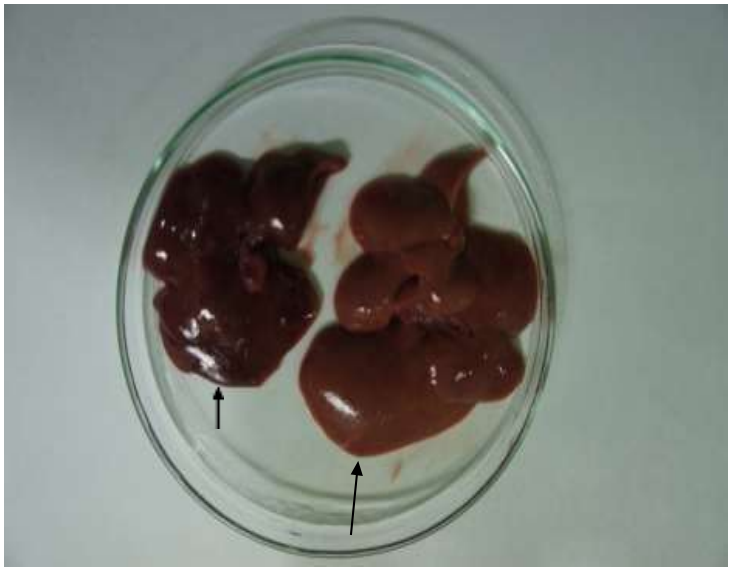
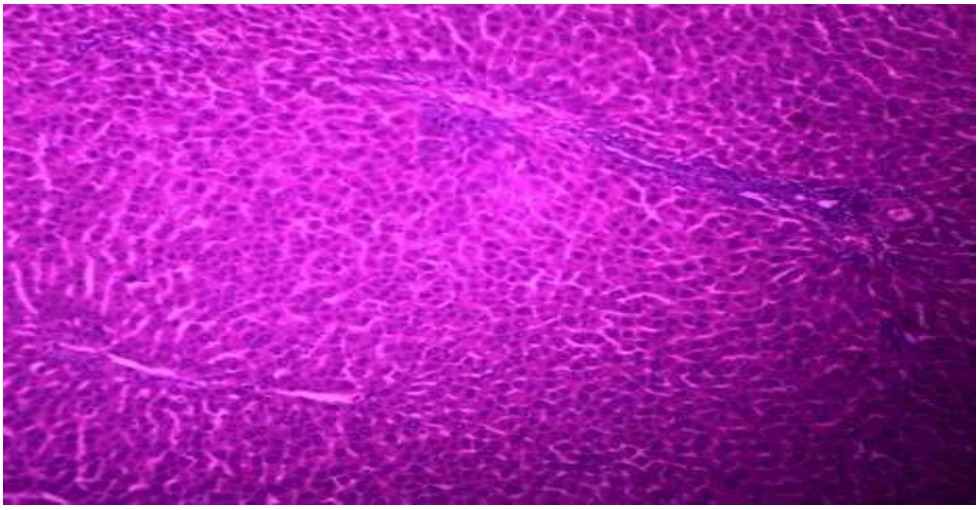
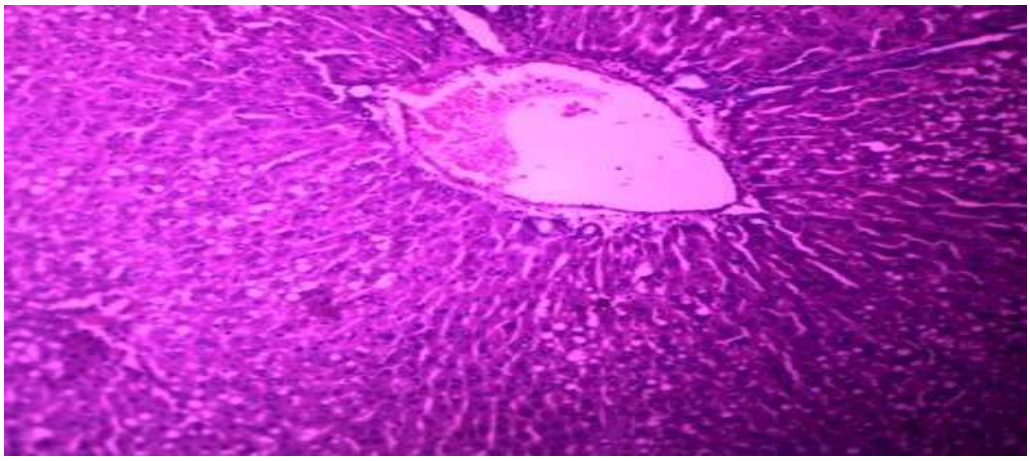


Figure 6: Photograph of liver tissue from normal control and HFD control groups



Section of liver (H&E) – Normal architecture with normal appearance of hepatic chords

Figure 7: Photomicrograph of Liver tissue from normal control group



Section of liver (H&E) – loss of architecture with presence of numerousfat vacuoles in the hepatocytes and dilated central vein; Sinusoidal spaces appear compressed

Figure 8: Photomicrograph of Liver tissue from HFD control group

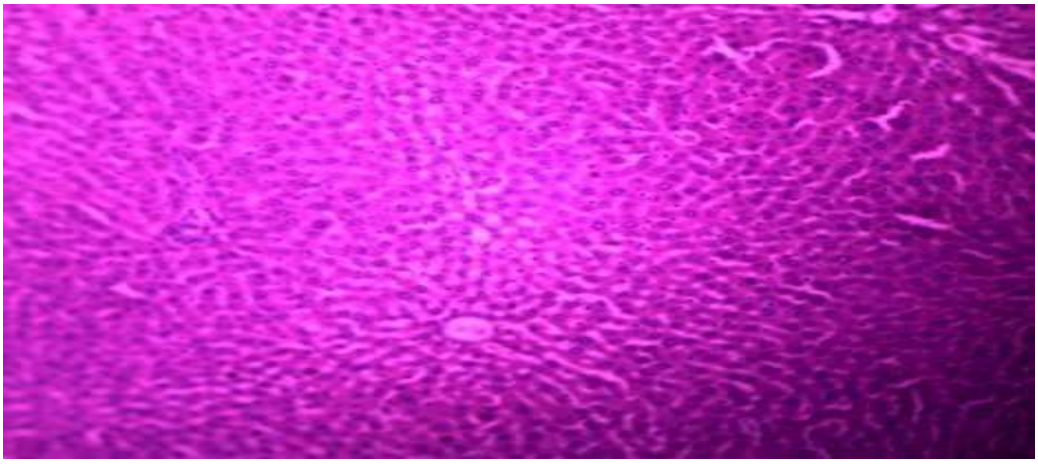
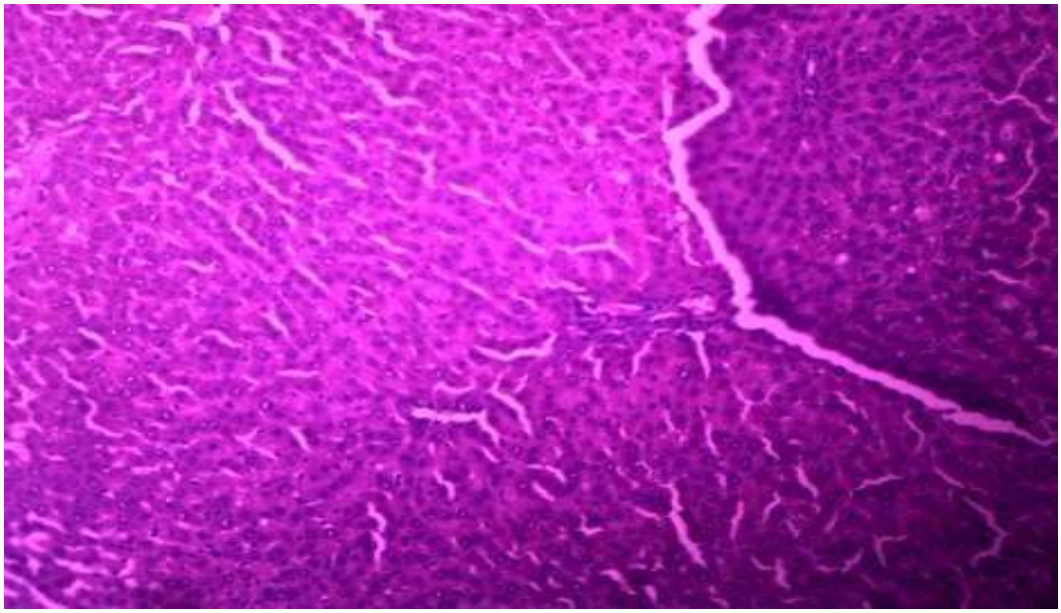


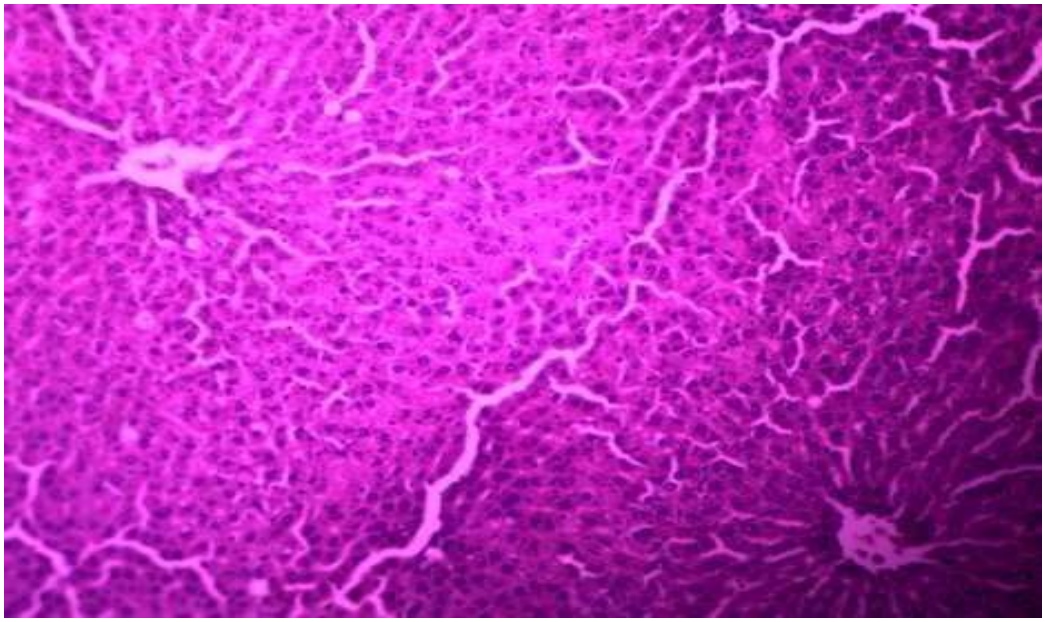
Figure 9: Photomicrograph of Liver tissue from *A. hirsutus* seed extract A (150mg/kg bwt) treatment group

Section of liver (H&E) – normal architecture with mild fatty infiltration; hepatic veins and Kupffer cells appear normal



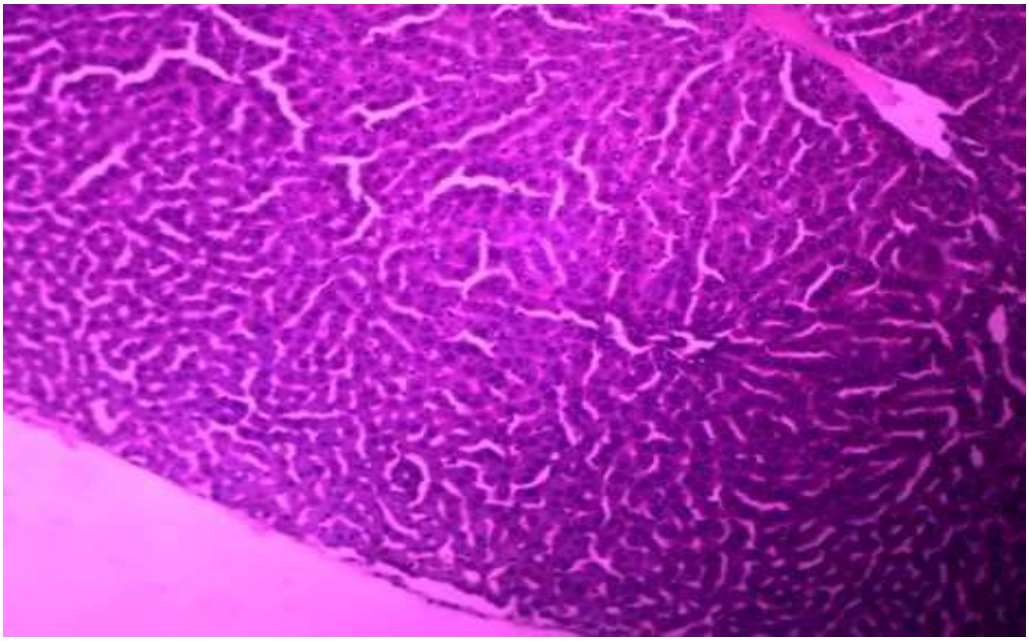
Section of liver (H& E) – loss of normal structure with mild fatty change inhepatocytes

Figure 10: Photomicrograph of Liver tissue from *A. hirsutus* seed extract B (150mg/kg bwt) treatment group



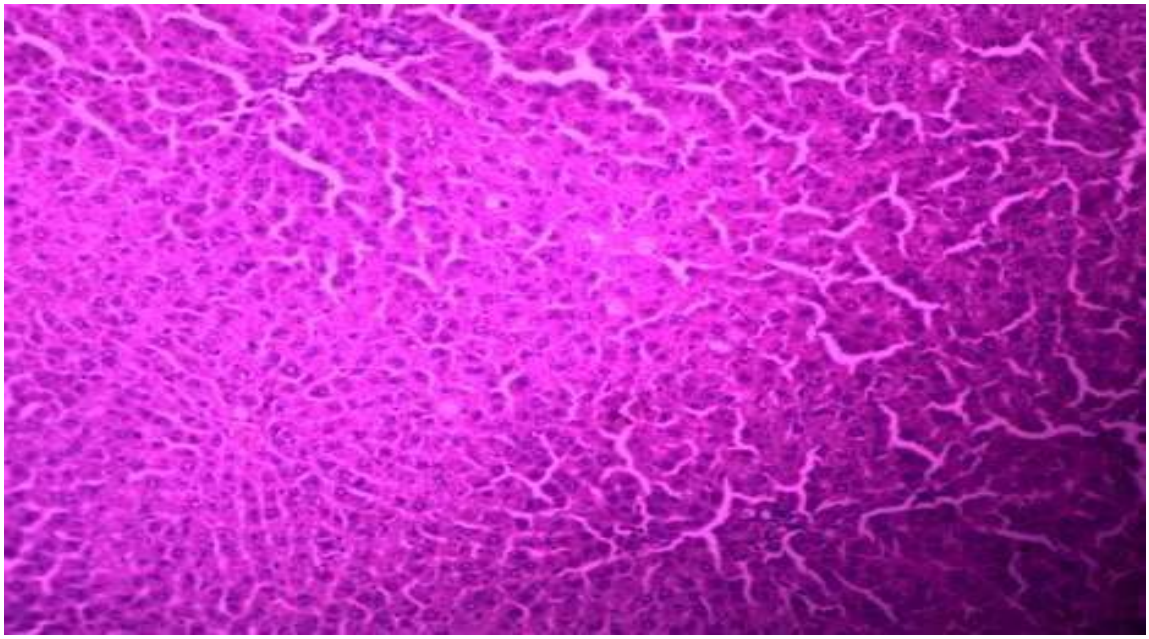
Section of liver (H&E) – normal architecture with mild fatty change

Figure 11: Photomicrograph of Liver tissue from *A. hirsutus* seed extract C (150mg/kg bwt) treatment group



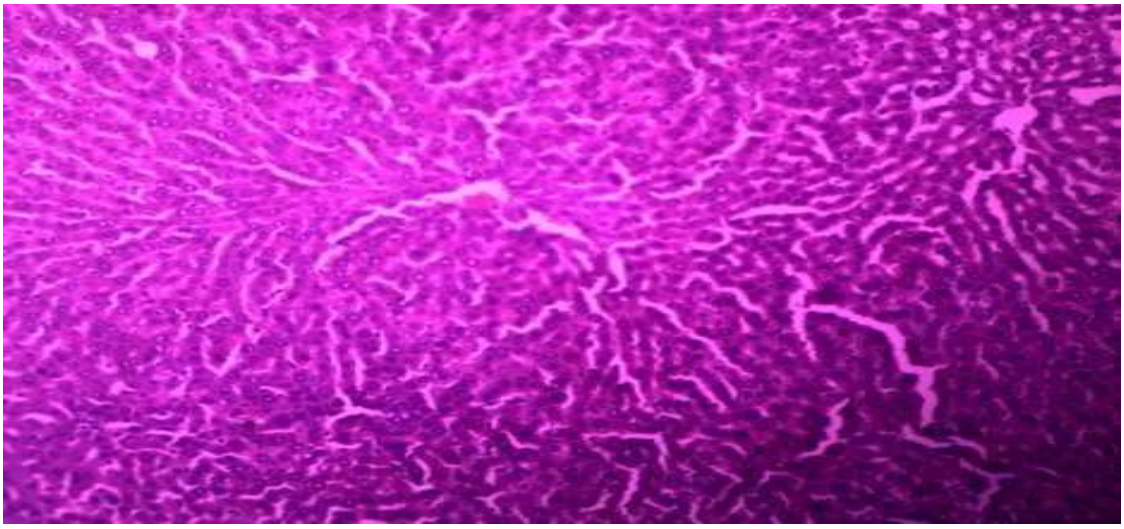
Section of liver (H&E) – mild loss of architecture with normal appearance ofhepatocytes

Figure 12: Photomicrograph of Liver tissue from *A. hirsutus* seed extract D (150mg/kg bwt) treatment group



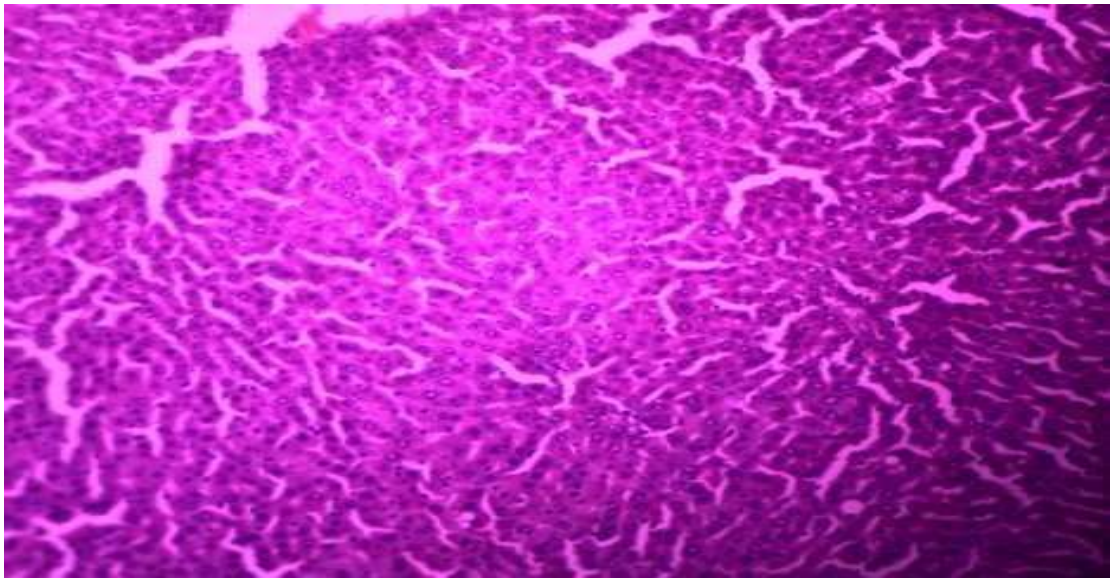
Section of liver (H&E) – normal architecture with very mild fatty infiltration ofhepatocytes

Figure 13: Photomicrograph of Liver tissue from *A. hirsutus* seed extract A (300mg/kg bwt) treatment group



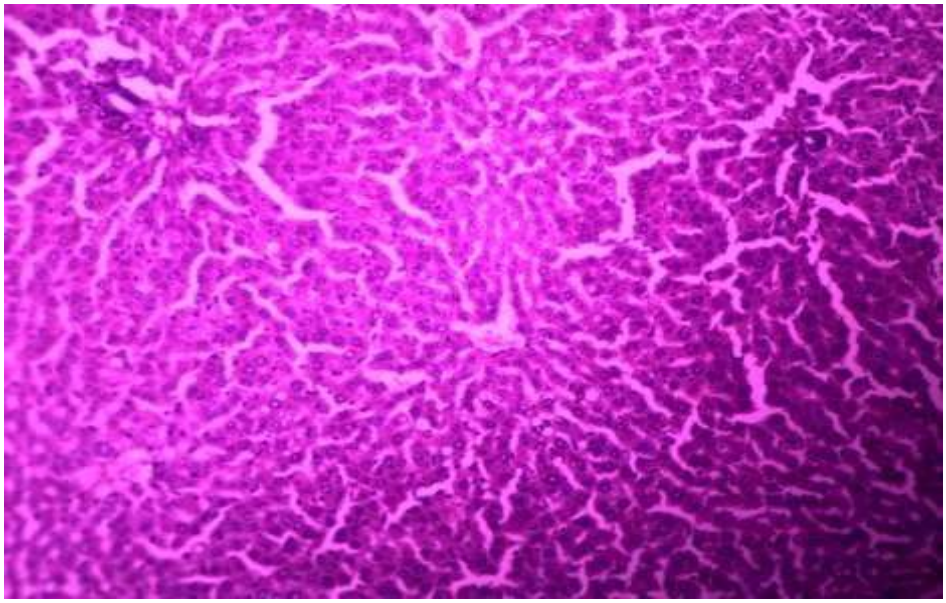
Section of liver (H&E) – partial loss of architecture with presence of a few fat vacuoles in the hepatocytes

Figure 14: Photomicrograph of Liver tissue from *A. hirsutus* seed extract B (300mg/kg bwt) treatment group



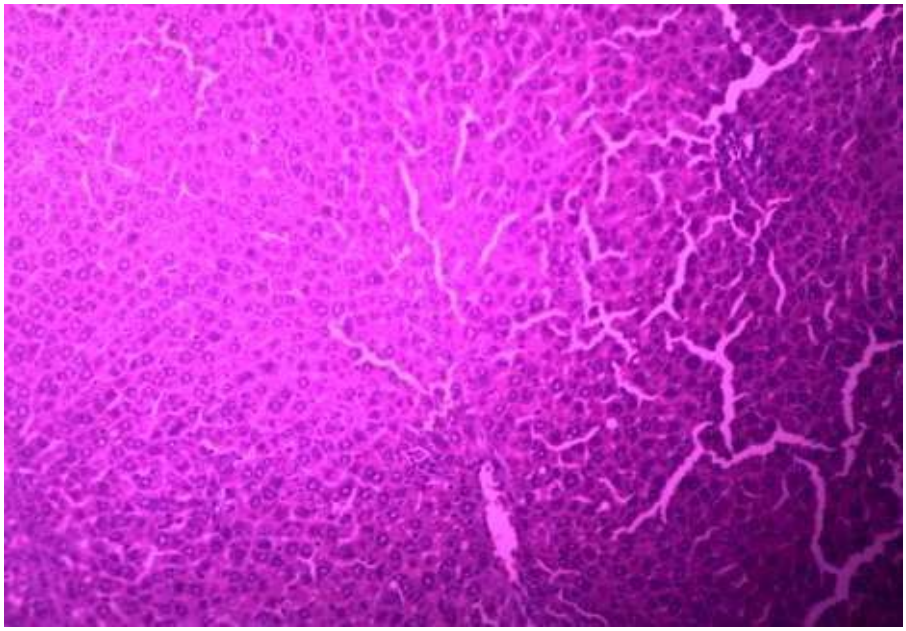
Section of liver (H&E) –mild loss of structure with almost normal hepatocytes

Figure 15: Photomicrograph of Liver tissue from *A. hirsutus* seed extract C (300mg/kg bwt) treatment group



Section of liver (H&E) – mild loss of architecture with presence offat vacuoles inthe hepatocytes

Figure 16: Photomicrograph of Liver tissue from *A. hirsutus* seed extract D (300mg/kg bwt) treatment group



Section of liver (H&E) – normal liver tissue with normal appearance of hepatocytes and hepatic vein

Figure 17: Photomicrograph of Liver tissue from Atorvastatin (10mg/kg bwt) treatment group

The objective of this study titled "Evaluation of Hypocholesterolemic potential of *Artocarpus hirsutus* seed extract in Wistar rats" was to assess potential of *A. hirsutus* seed extract to alleviate high fat diet induced hypercholesterolemia in laboratory rats.

Male Wistar Albino rats were utilized in this study. Animals were maintained under standard laboratory conditions (22 ± 3ºC room temperature and 50-60% humidity) with alternating light and dark cycles of 12 hrs. The rats were fed with pellet diet *ad libitium,* acclimatized to laboratory conditions for 7 days prior to the experiment and were divided into five groups of 6 rats each and received treatment .

Hypercholesterolemia was induced in all animals, except normal control group, using High Fat Diet (HFD). Treatment related changes in body weights were recorded. After completion of treatments, all animals were fasted overnight. Fasted rats were euthanized on next day by overdose of Thiopental sodium injection (intraperitoneal, i/p). Blood samples were collected immediately, by cardiac puncture and allowed to clot for 30 min at room temperature. Serum separated by centrifugation and used for the estimation of biochemical parameters like lipid profile, AST, ALT and ALP. The liver was collected immediately followed by fixation in 10% (w/v) buffered formalin and used for histological studies.

In conclusion, from the observations made in the present study with reference to serum lipid profile, liver function tests and histopathological analysis performed it could be concluded Artocarpus hirsutus seed extract at a dose of 300mg/kg was found to have a significant hypocholesterolemic effect on high fat diet induced Hypercholesterolemia model in Wistar rats.

Hence the present study indicates that *Artocarpus hirsutus* seed extract has a potential hypocholesterolemic action in high fat diet (HFD) induced hypercholeterolemic rats.

DISCUSSION

Hypercholesterolemia is a secondary metabolic dysregulation associated with diabetes. Besides the cause effect relationship with diabetes, elevated serum level of triglycerides, cholesterol and LDL are major risk factors for the premature development of cardiovascular disease like arthrosclerosis, hypertension, coronary heart disease etc. (Mani *et al*., 2012, Parasuraman *et al*., 2010). Increased plasma lipid levels mainly total cholesterol, triglycerides and LDL along with decrease in HDL are known to cause hyperlipidemia which is the reason for initiation and progression of atherosclerosis impasse (Sikarwar *et al*., 2012). Antihyperlipidemic agents having various pharmacological actions are being tested clinically. Elevated lipid levels result from increased absorption through the gut or enhanced endogenous synthesis and therefore two ways are feasible to reduce hyperlipidemia; to block endogenous synthesis or to decrease absorption.

Therapeutic potential of medicinal plants is mainly due to their phenolic compounds present in fruit, vegetables, nuts, seeds, stems, and flowers. The plants that show significant pharmacological activity and low toxicity need extensive screening. *Artocarpus hirsutus,* which

belongs to the family Moraceae, is one of the ancient plants in the world. It is found in Western Ghats of India and Malabar Coast, mountain belts of Karnataka, Kerala, and Tamil Nadu. The phytochemical analysis of *A. hirsutus* plant revealed that it is rich in major phytochemical compounds like alkaloids, flavonoids, glycosides, saponins, tannins, phenols, terpenoids, and carbohydrates (Jagtap *et al*., 2010 and Shanmuga priya *et al*., 2017).

The current study was designed to examine the cholesterol lowering activity of *A. hirsutus* seed extracts in hyperlipidemic rat model induced with 25% fat rich diet and details of parameters associated with hyperlipidemia (Cholesterol, Triglycerides, HDL & LDL and serum marker enzymes) were assessed.

The present study results elucidated high significant increase in serum total cholesterol, triglyceride and LDL-cholesterol concentrations in hypercholesterolemic control rats compared to normal rats. These results run in parallel with those of other investigators (Jang *et al.*, 2008). The hypocholesterolemic effect may be ascribed to the increased dietary cholesterol intake (Zulet *et al.*, 1999) and subsequently increased rate of intestinal cholesterol absorption (Mathe´, 1995). Increased serum concentration of triglycerides may be attributed to decreased clearance of triglycerides secondary to decreased activity of lipoprotein lipase (LPL) (Nofer *et al.*, 2002). The high level of LDL-cholesterol found in hypocholesterolemic rats may be attributed to a down regulation in LDL receptors by cholesterol and saturated fatty acids included in the diet (Mustad et al., 1997).

Treatment of hypercholesterolemic rats with *A. hirsutus* seed extracts induced marked significant decrease of serum total cholesterol, triglycerides and LDL-cholesterol concentrations as compared to the hypercholesterolemic rats. In general, Saponins are reported to precipitate cholesterol from micelles and interfere with enterohepatic circulation of bile acids making it unavailable for intestinal absorption, this forces liver to produce more bile from cholesterol (plasma) and hence the reduction in plasma cholesterol level. Saponins are also reported to lower triglycerides by inhibiting pancreatic lipoprotein lipase (Li *et al*., 2008). Similarly in this study also, the presence of both flavanoids and saponins in *A. hirsutus* seed extracts could have been contributed in reducing the levels of lipid status (TC, TG,).

High cholesterol diet increases plasma LDL levels and oxidative stress which results in the production of increased oxidized LDL. From the present study it is evident that HFD induced rats showed increased plasma LDL levels, when compared to normal rats. Supplementation with *A. hirsutus* seed extracts reduced the plasma LDL levels which could be due to reduction in plasma total cholesterol and increasing LDL receptor activity by the flavanoids present in the plant extract.

Also it could be presumed that the reduction of total cholesterol by extract could have been associated with a reduction of its LDL fraction, which is the target of several hypolipidemic drugs. In this study, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities were significantly high in high-fat fed diet than in normal rats, these results are in agreement with those of Sudhahar et al. (2007). This could be as a result of leakage of the enzymes into the serum as a result of damage to the integrity of the heart and liver. Elevated serum activity of these enzymes has been reported to be indicators of calculated risk of cardiovascular disease. According to Pincus and Schaffner (1996), AST and ALT are released into serum when there is severe hepatocellular injury. Therefore, elevated enzymes activity in serum of hypercholesterolemic control rats reflects the alterations in plasma membrane integrity and/or permeability. The declined enzymes activity secondary to drug and the *A. hirsutus* seed extracts treatments might be ascribed to their ability to maintain membrane integrity thereby restricting the leakage of these enzymes.

Significant elevation in body weight gain percent and absolute and relative liver weights were observed in high fat diet induced hypercholesterolemic animals which was in agreement with the observations of Mani *et al.* (2012). However during the 4 week study period, treatment with *A.hirsutus* seed extract resulted in significant normalization of body weight gain percent and absolute and relative weights of liver HFD fed animals. Moderate fatty change noted in the HFD control animals which were almost found alleviated in the drug and *A.hirsutus* seed extract treatment groups. *A.hirsutus* seed extract also resulted in normalizing the liver architecture quite appreciably as shown by histopathological examinations.

CONCLUSION

In conclusion, from the observations made in the present study with reference to serum lipid profile, liver function tests and histopathological analysis performed it could be concluded Artocarpus hirsutus seed extract at a dose of 300mg/kg was found to have a significant hypocholesterolemic effect on high fat diet induced Hypercholesterolemia model in Wistar rats. Hence the present study indicates that *Artocarpus hirsutus* seed extract has a potential hypocholesterolemic action in high fat diet (HFD) induced hypercholeterolemic rats.

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