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"ANTI-ATHEROSCLEROTIC ACTIVITY OF METHANOLIC EXTRACT OF LEAVES OF *MIRABILIS JALAPA* IN HIGH FAT INDUCED ATHEROSCLEROSIS MODEL RATS"

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ABSTRACT

The aim of the present study was to investigate the effect of methanolic extract of leaves of *Mirabilis Jalapa* in high fat diet induced atherosclerosis. Methanolic extract of leaves of *Mirabilis Jalapa* (MEMJ) were prepared and subjected to preliminary phytochemical investigations. Anti-atherosclerotic activity of MEMJ was evaluated in high fat diet (HFD) induced atherosclerosis model in Wister rats. Body weight changes, histopathology and lipid profile parameters were evaluated in HFD model. The phytochemical study revealed the presence of flavonoids compounds. MEMJ at a dose of 200 mg/kg and 400 mg/kg exhibited significant decrease in TG, TC, LDL, VLDL when compared to high-fat diet group. This investigation reveals that the extract-treated groups lower the serum lipoproteins-TC, TG, LDL and VLDL levels and increase in HDL significantly, which reduces the risk of coronary heart disease. This was further confirmed by histopathological study and calculated statistically to evaluate the anti-atherosclerosis effect of "*Mirabilis Jalapa*", and the high dose 400mg/kg body weight of MEMJ was found to more effective compared to the low dose 200mg/kg body weight of MEMJ.

KEYWORDS: *Mirabilis Jalapa*, High fat diet, High density lipoproteins, Low density lipoproteins Very Low density lipoproteins, Total Cholesterol, Triglyceride.

INTRODUCTION

Atherosclerosis is one of the major risk factors for coronary artery disease.[1] It is one of the most important cardiovascular diseases that involve vessels through the development of fatty

streaks and plaques.[2] There are a number of genetic, metabolic, and environmental factors involved in the formation and evolution of the atherosclerotic plaque. A well-known risk factor in humans is hypercholesterolemia, i.e., elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDLc), and other important contributors to this disease includes inflammation, oxidative stress and insulin resistance. Foods rich in saturated fat and cholesterol have been linked to elevations in circulating cholesterol levels.[1] Lipid-enriched diets are often used to induce or accelerate the rate of atherosclerotic lesion development in murine models of atherosclerosis.[3]

Hence, high fat diet is using to induce atherosclerosis for better understanding the disease and effect of treatment.

Plant-based compounds can help to treat or prevent Atherosclerosis through affecting the involved factors. Plant-based active compounds, including phenols, flavonoids, and antioxidants, can be effective on atherosclerosis predisposing factors and hence in preventing this disease and associated harmful complications, especially through reducing cholesterol, preventing increase in free radicals, and ultimately decreasing vascular plaque and vascular resistance. Hence, medicinal plants can contribute to treating atherosclerosis and preventing its progression through reducing cholesterolemia, free radicals, inflammation, vascular resistance, and certain enzymes.[2]

Mirabilis is a Genus of plants in the Family Nyctaginaceae and Kingdom Plantae known as the four-o'clocks or umbrellaworts. The best known species may be *Mirabilis Jalapa,* the plant most commonly called four o'clock**.** About 60 species in the world. It is commonly known as *Sanje mallige* (Karnataka); marvel of Peru / four-o'clocks (English); *Gulabakshi* (Maharastra*); Naalumani poovu*(Kerala).[4] Its flowers come in pink, red, yellow, white, and some bi-colors and have a slight vanilla scent.

Mirabilis Jalapa is widely used as a traditional medicine in the treatment of various ailments. Studies have evidenced its anti-bacterial, anti-viral, anti-fungal, anti-microbial, anti-inflammation, anti-stress, diuretic and anti-oxidant activities .Chemical analysis of various parts of M. Jalapa revealed the presence of alkaloids, flavonoids, phenols, steroids, triterpenes, glycosides, tannins, saponins and lignins. The complete study of these compounds from TLC visualized alanine, arabinose, campesterol, daucosterol and dopamine, d-glucan, hexacon-1-ol, indicaxanthin, isobetanin, 6-methoxyboeravinone, C-

methylabronisoflavones, miraxanthins, n-dotriacontane, n-nonacosane, n-pentacosane, n-triacontane.[5] Leaves of *Mirabilis Jalapa* has Purgative and emetic properties[6] and also used for treating gastrointestinal disorders, including dysentery, diarrhea, muscle pain and abdominal colic[7], Constipation[8], amenorrhea and dysmenorrhea in women[9], jaundice[10], hepatitis[11], and Juice of leaves is used as eye drop to soothe eye inflammation. Boiled Leaves are consumed to reduce body pains. Tuber is administered in small quantities to cure piles.[12] Stem with leaves are utilized for depigmentation.[13] Extract of roots has Hypolipidemic and hypoglycemic activity[14], Leaves of *Mirabilis Jalapa* are applied on external wounds until recovery.[15] The flowers are used in food coloring. The leaves may be eaten cooked as well, but only as an emergency food. An edible crimson dye is obtained from the flowers to color cakes and jellies.[16] The seeds are considered poisonous.[17]

Hence, the present study was aimed to demonstrate the anti-atherosclerotic activity of leaves of methanolic extract of *Mirabilis Jalapa* in high fat diet induced atherosclerosis rats.

MATERIALS AND METHODS

Drugs and chemicals

Chloroform, Saturated picric acid, 10% Formalin, Methanol, cholesterol 2%, Vanaspathi 1 %, Sucrose 40%, Coconut oil 10%, Pentobartibotne sodium, Atorvastatin 10mg/kg.

Collection and Authentication of Plant Materials

The whole fresh plants materials of *Mirabilis Jalapa* were collected from local areas of Bangalore, Karnataka state, India in the month of August 2021. This plant species were authenticated by Dr.K.R.Kavitha, Associate Professor, and HOD Department of Botany. The plant was identified by a botanist, and voucher specimen was deposited in Rajiv Gandhi University of Health Sciences and a copy has been preserved for the future reference at the Department of pharmacology, Karnataka College of pharmacy. The collected M.*Jalapa* whole plant was washed thoroughly with tap water to remove the adhering soil, mud, and debris. All old insect damage or fungus infected leaves, and flowers were removed. The plant material (leaves) was cut into small pieces and air-dried thoroughly under shade (at room temperature) for 1 week to avoid direct loss of phytoconstituents from sunlight. The shade dried materials were coarsely powdered using blender. The powder was stored in an air tight container and was protected from light.

Preparation of plant extract

The course ground powder of *Mirabilis Jalapa* was transferred in to the extraction glass and the plant material was loaded into the main chamber of the soxhlet extractor. Then this part of the extractor is connected into the round bottom flask containing extraction solvent. The grinded course powder was packed in the tightly in the soxhlet extractor and methanol solvent was used for the extraction of the *Mirabilis Jalapa* leaves powder.

In this extraction process 1000ml solvent was used and was carried for about 6hr. The extract was again re-extracted under the same conditions to ensure complete extraction. The methanol was filled into the solvent vessel and extracted at a temperature of 750 c for 6h. The solvent was drained into a beaker by opening the spigot on the soxhlet extractor. The solvent was removed from the extractor and dried. The extract was then stored in dry airtight bottles for the pharmacological studies. The portion of the extract which is non- soluble remains in the thimble and it was discarded.[18]

Experimental Animals

The Wistar rat is currently one of the most popular rats used for laboratory research. It is characterized by its wide head, long ears, and having a tail length that is always less than its body length. Wistar rats are more active than others like Sprague Dawley rats. Adult Wistar rats (150-250gm) was used to evaluate the Anti-atherosclerotic and anti-oxidant activity. The animal was kept under standard environmental conditions of room temperature (220 ±20 C), relative humidity (50% ± 5%) and 12 h light and dark cycle. All the rats was acclimatized to the laboratory environment 5 days prior to experiment. The animals was fasted overnight just prior to the experiment but was allowed for free access to drinking water. The study was conducted after obtaining ethical committee clearance from the Institutional Animal Ethics Committee. The study protocols was duly approved by the Institutional Animal Ethics Committee (IAEC) **REG NO; KCP/IAEEC/09/21-22/12/18-12-21** at Karnataka College of Pharmacy, Bangalore. A study was performed in accordance with the CPCSEA.[19]

Phytochemical test[20, 21]

The phytochemical screening of the methanolic extract of *Mirabilis Jalapa* was carried out in order to ascertain the presence of its constituents. The filtrates obtained were used for the screening of secondary metabolites following standard procedures (Kokate et al., 2009; Evansand Trease 2002; Khandelwal, 1995; De et al., 2010).

Acute toxicity study[22]

Acute toxicity study was conducted for the methanolic extract leaves of *Mirabilis Jalapa as* per OECD guidelines 425 using Swiss albino mice. Each animal was administered methanolic extracts by oral route. The animals were observed for any changes continuously for the first 2 h and up to 24 h for mortality.

Preparation of Dose

A dose of 1/5th and 1/10th of 2000mg/kg were considered to be high dose and low dose prepared by suspending sterile water.

High fat diet induced atherosclerosis

Normal animal food pellets was crushed in mortar and pestle to make into small pieces and then grinded into fine powder in mixer grinder. The other ingredients i.e. cholesterol 2%, Vanaspathi 1%, sucrose 40%, and coconut oil 10% was added in the mixer grinder in an ascending order of their quantity and mixed well. This dried powder was then mixed with same quantity of water every time to make small balls of feed and later this was stored in self-sealing plastic covers inrefrigerator at 2°C to 8°C.[23]

Method

Animals are divided into 5 groups each group have six animals.

Group I (n=6): Normal control group, rats were treated with normal saline solution orally for 21days.

Group II (n=6): Atherosclerotic control group, rats were treated with high fat diet (FD) for 21days.[24]

Group III (n=6): Standard group, rats were treated with Atorvastatin (10mg/kg/p.o), for 14 consecutive days, along with high fat diet for 21 day.[25]

Group IV (n=6): Test group 1, rats were treated with "*Mirabilis Jalapa"* low dose (200mg/kg/p. o) plant extract, for 14 consecutive days, along with high fat diet (for 21 days).[26]

Group V (n=6): Test group 2, rats were treated with "*Mirabilis Jalapa"* high dose (400mg/kg/p.o) plant extract, for 14 consecutive days, along with high fat diet for 21 days.[26]

Physical parameters

Body weight

The weight of the animals was measured before starting and at the end of the experiment andchange in body weight was calculated.

Lipid parameters: At the end of the experimental studies animals were fasted for 12 hrs and the blood was collected by cardiac puncture under pentobartibotne sodium euthanasia. Lipid parameter was evaluated Total cholesterol (TC), low density lipoprotein.

(LDL), Very low density lipoprotein (VLDL), High density lipoprotein (HDL) and Triglycerides(TAG), was evaluated from the serum.[27]

Histopathological analysis- The liver was isolated and preserved in 10% formalin solution. And the liver section was evaluated for histopathology to assess architectural changes.

Statistical analysis. The results was expressed as mean ± S.E.M from n=6 rats in each group. The significance of difference among the groups was assessed using one-way analysis of variance (ANOVA) followed by Turkey's multiple comparison test compared disease control vs all groups, The values were considered statistically significant when $p<0.05$.

RESULT

Preparation of extract

The dried powder of leaves of *Mirabilis Jalapa* was successively extracted with methanol and the percentage yield of the extract obtained was recorded. The extract had a characteristic smell and the color of extract was ranging from dark green.

Percentage yield and physical characters of *Mirabilis Jalapa.*

Table 1: Percentage yield of the leaves of *Mirabilis Jalapa* Extract.

Plant extracted in	Percentage Yield	Colour	Nature
Methanol	5.20%	Dark Green	amorphous

Phytochemical Screening of *Mirabilis Jalapa*

The phytochemical constituent tests of crude extract of *Mirabilis Jalapa* were carried out.

Table 2: Phytochemical test.

Sl.No	Constituents	Tests	Result
1.	Flavonoid	Zinc Hydrochloric acid test	+
		Lead acetate test	+
		Shinodas test	+
		Ferric chloride test	+
2.	Sterols	Liebermann burchard test	+
		Salkowski test	+
3.	Terpenoids	Terpenoid test	+
4.	Alkaloids	Mayer's test	+
		Wagers test	+
		Drangendoffs test	+
		Hager's test	+
		Tannic acid test	+
5.	Saponin	Foam test	+
6.	Tannin	Ferric chloride test	+
		Gelatin test	+
		Lead acetate test	+
		Alkaline reagent test	+
7.	Phenols	Ellagic acid test	+
		Phenols test	+
8.	Glycosides	Keller killiani test	+
		Concentrated sulphuric acid	+
		Molischs test	+

Where :(+) represents - present and, (-) represents – absent

Result of Acute Oral Toxicity Study

The LD50 of the extract of *Mirabilis Jalapa* was found to be 2000mg/kg after performing the acute oral toxicity studies. 1/10th and 1/5th of the same dose was selected (200mg/kg and 400mg/kg respectively) and the experiment was carried out.

Effect of MEMJ on the average body weight of HFD induced atherosclerotic rats

Table No 3: Effect of graded oral doses of MEMJ on average body weight in HFD induced rats.

Sl. No.	GROUPS	Average body weight (g) of rats	
		Day 0	Day 21st
1	Group 1	145.30 ±1.60	147.92 ± 0.21
2	Group 2	155.00 ±0.88	169.01 ± 0.70
3	Group 3	159.66 ±0.51	162.40± 0.69
4	Group 4	155.60 ±1.46	159.92 ± 0.19
5	Group 5	159.33 ±0.76	160.40 ± 0.46

The data are expressed as Mean ±S.E.M (n=6) rats in each group

The highest body weight was found in the disease control group (**168.01 ± 0.70)** when compared with normal control (**147.92 ± 0.21),**. This increase in the body weight was due to greater lipid deposition in the body tissue of the animal.

Effect of the HFD, standard and test drug on Triglyceride level

Table No. 4- Effect of graded oral doses of MEMJ on the Triglyceride in HFD induced rat. Normal TGs level (below 200mg/dl)

Sl. No.	GROUPS	Triglyceride (mg/dl)
1.	Group 1	122.7±1.048
2.	Group 2	347.7±1.409
3.	Group 3	189.1±1.162****
4.	Group 4	204.6±3.210****
5.	Group 5	179.6±0.9721****

Values are expressed as Mean ± SEM (n=6) rats in each group, *, **, ***, ****, ns - Mean values are significantly different when compared with Disease control mean values at P<0.05, P<0.01, P<0.001, P<0.0001 and non-significant, respectively using one way Anova followed by tukey‟s test.

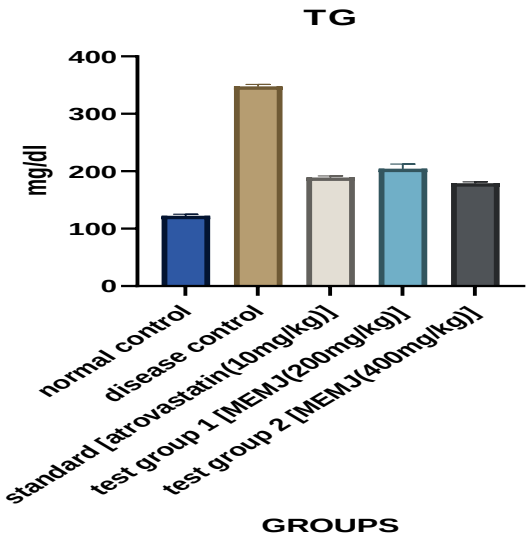

Figure 1: **Triglyceride level of various groups**

Due to induction of the HFD, TG level resulted in significant raise in the disease control group (**347.7±1.409**) compared to the normal control group (**122.7±1.048**). Treatment with MEMJ resulted in significant decrease in TG compared to disease group, (**204.6±3.210**) for 200mg/kg, and (**179.6±0.9721**) for 400mg/kg. The standard group showed significantly reduced levels (**189.1±1.162**) compared to disease control. (Figure 1.)

Effect of the HFD, standard and test drug on Total Cholesterol

Table No.5- Effect of graded oral doses of MEMJ on the Total Cholesterol level in HFD induced rat.

Sl. No.	GROUPS	Total Cholesterol (mg/dl)
1.	Group 1	141.4 ±1.090
2.	Group 2	256.2±1.284
3.	Group 3	167.6±0.7623 ****
4	Group 4	176.1±1.207****
5.	Group 5	158.6±1.797****

Normal TC level (below 200mg/dl)

Values are expressed as Mean ± SEM (n=6) rats in each group, *, **, ***, ****, ns - Mean values are significantly different when compared with Disease control mean values at P<0.05, P<0.01, P<0.001, P<0.0001 and non-significant, respectively using one way Anova followed by tukey‟s test.

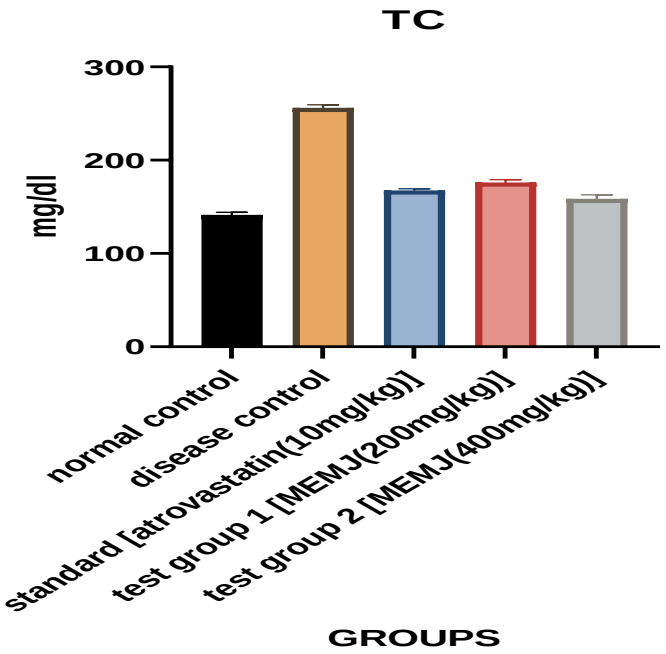

Figure 2: **Total cholesterol level of various groups**.

Due to induction of the HFD, TC level resulted in significant raise in the disease control group (**256.2±1.284**) compared to the normal control group (**141.4 ±1.090**). Treatment with MEMJ resulted in significant decrease in TC compared to disease group, (**176.1±1.207**) for 200mg/kg, and (**158.6±1.797**) for 400mg/kg. The standard group showed significantly reduced levels (**167.6±0.7623**) compared to disease control. (Figure 2.)

Effect of the HDL, standard and test drug on HDL level

Table No.6-Effect of graded oral doses of MEMJ on the HDL level HFD induced rat.

Sl. No.	GROUPS	HDL(mg/ dl)
1.	Group 1	47.73±1.148
2.	Group 2	27.72±0.9323
3.	Group 3	38.16±1.395**
4.	Group 4	28.58±1.261 ^{ns}
5.	Group 5	36.59±1.295**

Normal HDL cholesterol level (40 to 59 mg/dl).

Values are expressed as Mean ± SEM (n=6) rats in each group, *, **, ***, ****, ns - Mean values are significantly different when compared with Disease control mean values at P<0.05, P<0.01, P<0.001, P<0.0001 and non-significant, respectively using one way Anova followed by tukey‟s test.

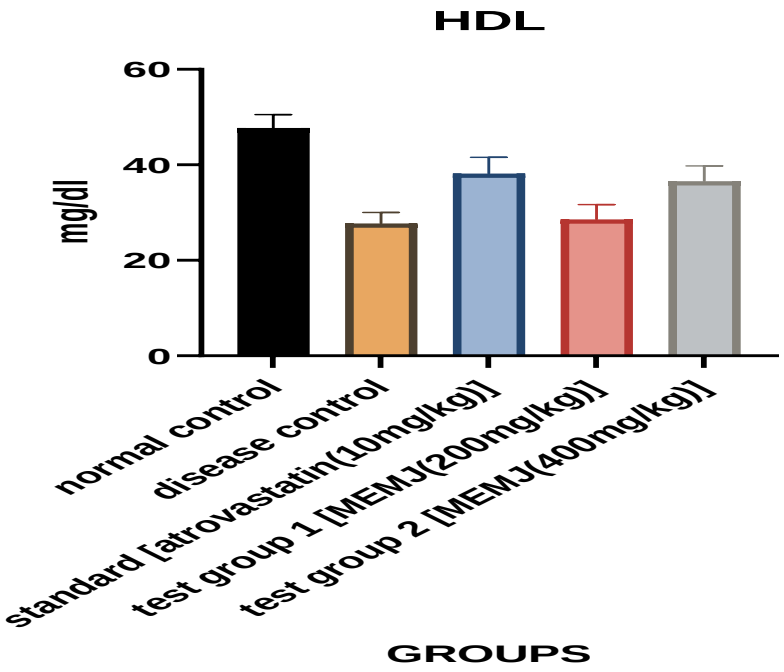

Figure 3: **HDL levels of various groups.**

Due to induction of the HFD, HDL level resulted in significant decrease in the disease control group (**27.72±0.9323**) compared to the normal control group (**47.73±1.148**). Treatment with MEMJ showed non-significant in HDL compared to disease group, (**28.58±1.261^{ns}**) for 200mg/kg, and significant increase in HDL level (**36.59±1.295**) for 400mg/kg. The standard group showed significantly increase in HDL levels (**38.16±1.395**) compared to disease control. (Figure 3.)

Effect of the HFD, standard and test drug on LDL levels

Table No.7-Effect of graded oral doses of MEMJ on the LDL levels in HFD induced rats.

Sl. No.	GROUPS	LDL(mg/ dl)
1.	Group 1	99.97±0.9443
2.	Group 2	172.6±1.103
3.	Group 3	118.2±0.8712****
4.	Group 4	141.6±1.341****
5.	Group 5	129.7±1.008****

Normal LDL Cholesterol level (below 100 to 129 mg/dl)

Values are expressed as Mean ± SEM (n=6) rats in each group, *, **, ***, ****, ns - Mean values are significantly different when compared with Disease control mean values at P<0.05, P<0.01, P<0.001, P<0.0001 and non-significant, respectively using one way Anova followed by tukey‟s test.

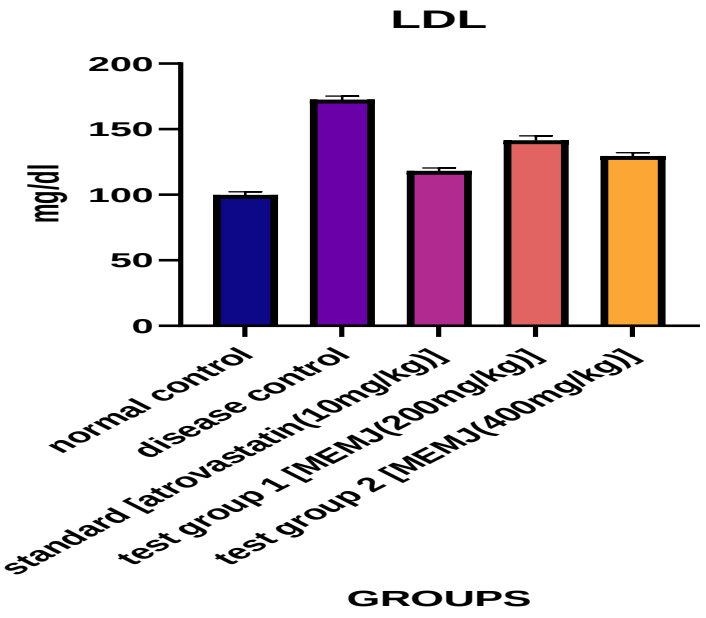

Figure 4: **LDL levels of various groups.**

Due to induction of the HFD, LDL level resulted in significant raise in the disease control group (**172.6±1.103**) compared to the normal control group (**99.97±0.9443**). Treatment with MEMJ resulted in significant decrease in LDL compared to disease group, (**141.6±1.341**) for 200mg/kg, and (**129.7±1.008**) for 400mg/kg. The standard group showed significantly reduced levels (**118.2±0.8712**) compared to disease control. (Figure 4.)

Effect of the HFD, standard and test drug on VLDL level

Table No.8: Effect of graded oral doses of MEMJ on the VLDL level in HFD induced rat.

Sl. No.	GROUPS	VLDL(mg/dl)
1.	Group 1	24.20 ±0.9636
2	Group 2	43.47±1.227
3.	Group 3	34.26±1.321*
4.	Group 4	35.26±1.044 **
5.	Group 5	31.50±0.8760****

Normal VLDL cholesterol level (below 30mg/dl)

Values are expressed as Mean ± SEM (n=6) rats in each group, *, **, ***, ****, ns - Mean values are significantly different when compared with Disease control mean values at P<0.05, P<0.01, P<0.001, P<0.0001 and non-significant, respectively using one way Anova followed by tukey‟s test.

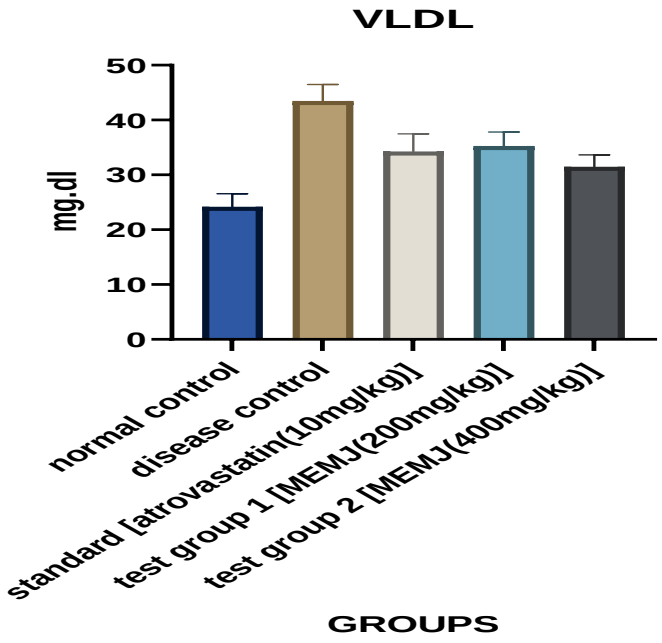

Figure 5: **VLDL levels of various groups.**

Due to induction of the HFD, VLDL level resulted in significant raise in the disease control group (**43.47±1.227**) compared to the normal control group (**24.20 ±0.9636**). Treatment with MEMJ resulted in significant decrease in VLDL compared to disease group, (**35.26±1.044**) for 200mg/kg, and (**31.50±0.8760**) for 400mg/kg. The standard group showed significantly reduced levels (**34.26±1.321**) compared to disease control. (Figure 5.)

HISTOPATHOLOGICAL ANALYSIS

Effect of normal saline

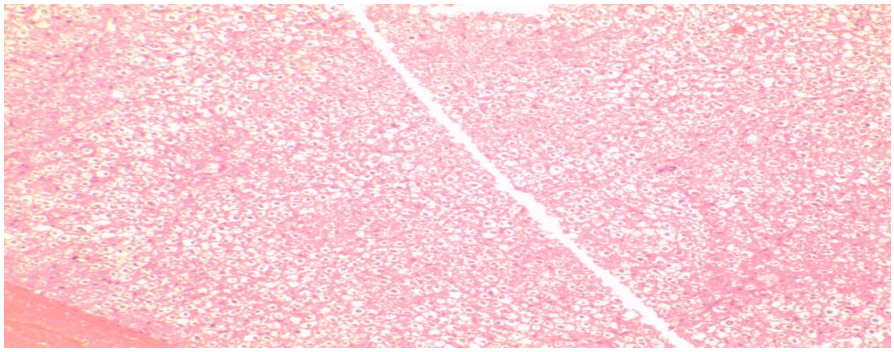

Fig 6: Effect of Normal saline (10ml/kg).

Group I Liver showing normal architecture of hepatocytes arranged cord like manner around the central vein with cytoplasm staining red and vesicular type of nucleus staining blue.

Effect of High fat diet on liver

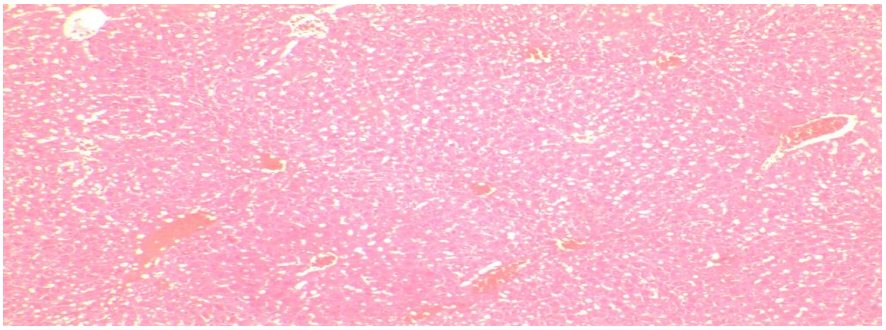

Fig 7: Effect of high fat diet on liver.

Group II - Liver showing mild vacuolar degeneration of hepatocytes with unstained vacuoles inside, indicating lack of cytoplasm with compact core and focal inflammation of the portal.

Effect of High fat diet+ Atorvastatin (10mg/Kg) on liver

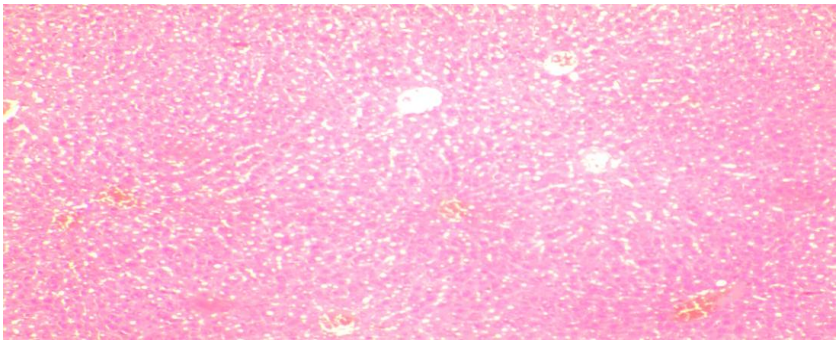

Fig 8: Effect of high fat diet+ Atorvastatin (10mg/Kg) on liver.

Group III - Normal liver architecture with condensed nucleus, with minor artery degeneration.

Effect of MEMJ (200 mg/kg) + High fat diet on liver

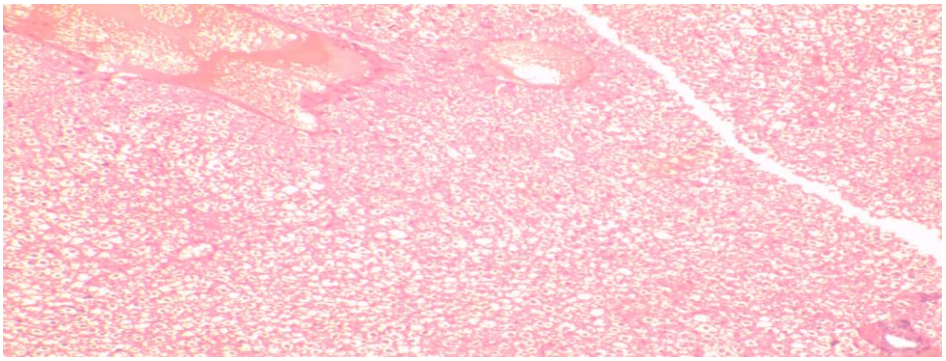

Fig 13: **Effect of MEMJ (200 mg/kg) + High fat diet on liver.**

Group IV - Liver showing mild vacuolar degeneration with condensed nucleus of hepatocytes. And no necrosis, inflammation have been reported.

Effect of MEMJ (400mg/kg) + High fat diet on liver

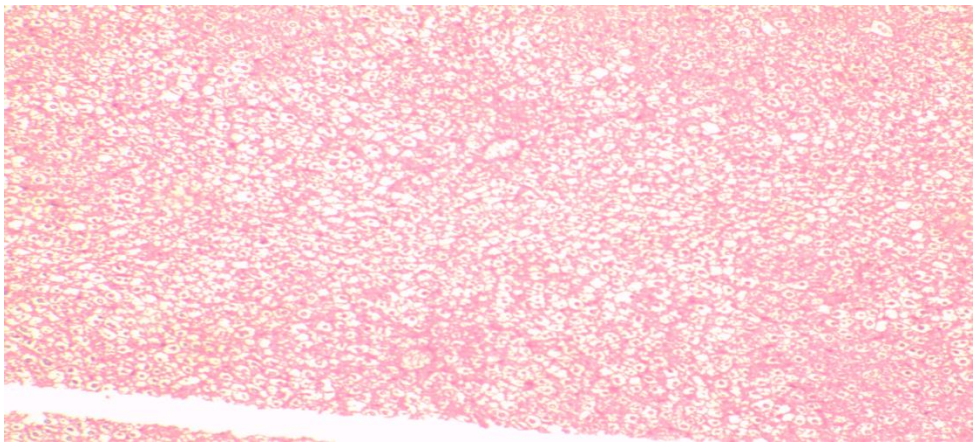

Fig 9: Effect of MEMJ (200 mg/kg) + High fat diet on liver.

Group V- Liver with normal arrangement, cord arranged on hepatocytes along the central vein with a red and vesicular cytoplasm of the nucleus.

DISCUSSION

The present study showed that dietary treatment of rats with high fat diets caused atherosclerotic lesions in an animal model, and these findings were in accordance with earlier studies. Excess amount of cholesterol feeding causes rapid hyperlipidemia and atherosclerosis. The statin drugs were accepted as cholesterol-lowering drug in humans. Hence, the standard group was used to compare the effectiveness of the drug in reducing

plasma cholesterol levels.[28]

The animal fed with only high-fat diet group for 21 days showed significant increase in the total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein when compared with the normal group.

This increase in TC and LDL was due to the increase in cholesterol absorption in the intestines. Based on the present data, the ATR treated group showed notable decrease in TC, TG, LDL, and VLDL levels. MEMJ at a dose of 200 mg/kg and 400 mg/kg showed significant dose-dependent decrease in TC, TG, LDL, VLDL levels when compared to high fat diet group.

This investigation reveals that the plant extract feeding lowers the serum TC, TG, VLDL and LDL levels significantly, which reduces the risk of coronary heart disease. In the present study, animals treated with ATR and high-fat diet showed significant increase in high-density lipoprotein (HDL) level. MEMJ of 400 mg/kg showed progressive increase in HDL level when compared to high-fat diet group. *Mirabilis Jalapa* leaves extract-treated groups had restored the HDL-C level to the normal.

The food intake and body weight in all groups were increased throughout the experimental period. At the end of study, the highest body weight was found in the high-fat diet group. This increase in the body weight was due to greater lipid deposition in the body tissue of the animal in accordance with a previous study by Lee et al.[29] and Weintraub.[30]

ATR-treated group showed reduced food intake and body weight. MEMJ at a dose of 200 mg/kg and 400 mg/kg showed dose-dependent decrease in the food intake and body weight when compared to the high-fat diet group.

In histopathological studies, the liver in the high-fat diet group animals showed mild vacuolar degeneration of hepatocytes with unstained vacuoles inside, indicating lack of cytoplasm with compact core and focal inflammation of the portal.

Therefore, it was clear that the high-fat diet group showed notable increase in lipid composition levels in the liver. ATR-treated group had showed Normal liver architecture with condensed nucleus, with minor artery degeneration.

MEMJ-treated group 1(low dose 200mg/kg) liver showed Liver showing mild vacuolar degeneration with condensed nucleus of hepatocytes but, MEMJ-treated group 2 (high dose 400mg/kg) liver showing normal arrangement, cord arranged on hepatocytes along the central vein with a red and vesicular cytoplasm of the nucleus. MEMJ high dose 400 mg/kg shows effectiveness of drug against hyperlipidemia and atherosclerosis.

CONCLUSION

The cholesterol lowering effect of the plant extract might be decrease in intestinal absorption of cholesterol by increasing in the fecal excretion of neutral lipids.[31] The anti-atherosclerosis activity of MEMJ might be due to the presence of phytoconstituents. Thus, it validated the traditional use as an ethno medicine against atherosclerosis. However, further studies are needed to identify and characterize the phytoconstituents from MEMJ and also to explore the exact mechanism to act as anti-atherosclerotic, before being establish it in clinical setting.

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