DOSE DEPENDENT ANTIHYPERLIPIDEMIC ACTIVITY OF ETHANOLIC EXTRACT OF *MENTHA ARVENSIS* LEAVES IN TRITON AND HIGH CHOLESTEROL DIET INDUCED RATS

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ABSTRACT

A study was undertaken to evaluate antihyperlipidemic activity of ethanolic extract of leaves of *Mentha arvensis* in Triton and high cholesterol diet induced hyperlipidemic male albino Wstar rats. Acute hyperlipidemia was induced by administration of Triton WR-1339 (100 mg / kg i.v.) to the male albino Wstar rats. In chronic models; the animals were fed with high cholesterol diet for a period of 10 days. EEMA leaves at a dose of 200 and 400 mg/kg of body weight were administered at a single dose per day to the hyperlipidemic induced rats for a period of 14 days. In hyperlipidemic rats there is significant increase in TC, TG, LDL, VLDL level and significant decrease in HDL level, but after post treatment with EEMA, there was a significant decrease in TC, TG, LDL, VLDL and increase in HDL level. Post treatment with EEMA *leaves* lowered levels of total protein and triglycerides.

Key words: Triton WR 1339, MA, Nicotinic acid etc.

INTRODUCTION

The human body is complex machinery and various organ and organ system contribute for maintaining the homeostasis. Any undesirable change occuring will disturb the balance, resulting in a diseased state. The lung and other tissues contain polyunsaturated fatty acids (PUFAs). PUFA is the main component of membrane lipids and is susceptible to peroxidation as a result of oxidative stress leading to loss of functional integrity of the cell membranes. Complication in hyperlipidemia is due to the changes in the level of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and high density lipoprotein levels (HDL). The same way, the change in the level of lipids will lead to many complications[1]. but lipids are naturally occurring molecules, which are the main component of the cell membrane. They act as blood transporter and their main function is energy storage[2-3].

Hyperlipidemia is the greatest risk factor of coronary heart diseases. Hyperlipidemia is due to abnormally elevated levels of all lipids and/or lipoproteins in the blood. Coronary heart disease, atherosclerosis, stroke, and hyperlipidemia are the primary causes of death. Hyperlipidemia associated lipid disorders are considered to cause atherosclerotic cardiovascular disease .Among these hypercholesterolemia and hypertriglyceridemia are closely related to ischemic heart disease[4].

The American Heart Association has identified the primary risk factor associated with atherosclerosis to be the elevated levels of cholesterol and triglyceride in the blood. Therapist considers hyperlipidemia treatment to be one of the major approaches towards decelerating the atherogenic process. Atherosclerosis is referred to as a “silent killer”, which is one of the leading causes of death in the developing countries like India. The cardiovascular disease risk arises from increased LDL cholesterol and is supported by observations that cholesterol-lowering therapy greatly diminishes the clinical manifestations of atherosclerosis, particularly since the advent of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (i.e.statins) that profoundly lower LDL cholesterol. In contrast to the situation with LDL cholesterol, the relation between HDL cholesterol and atherosclerosis is an inverse one[5-7].

Atherosclerosis, or hardening of the arteries, is mainly due to high lipid levels. the arteries are normally smooth and unobstructed on the inside, but with age, a sticky substance called plaque forms in the walls of the arteries.

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Formation of plaque is mainly due to variation in the level of lipids and other materials circulating in the blood. Arteries can narrow and stiffen as more plaque builds up. Heart disease, stroke, and other vascular diseases are mainly due to the atherosclerosis. Fortunately, it is possible to reduce lipid levels and, therefore, prevent or slow the progression of atherosclerosis. Lifestyle changes like exercising and eating a healthy diet can also lower your lipid levels and are often the first step in treatment of hyperlipidemia [8].

WHO reports 56% of the cardiovascular diseases that are from high blood cholesterol and causes about 4.4 million deaths per year. Currently available antihyperlipidemic drugs (statins, fibrates) have been associated with a number of side effects. Hyperuricemia, diarrhea, nausea, myositis, gastric irritation, flushing, dry skin and abnormal liver function present.

The use of alternative medicines Especially the consumption of Phytochemical have been rapidly increasing worldwide. As herbal medicines are less damaging than synthetic drugs and have better Compatibility is thus improved patient[8- 9].

Triton WR-1339, a non-ionic detergent (oxyethylated tertiary octyl phenol formaldehyde polymer), has been widely used to induce acute hyperlipidemia in animal models in order to screen natural and synthetic drugs and to study cholesterol and triacylglycerol metabolism. The accumulation of plasma lipids by Triton appears to be especially due to the inhibition of lipoprotein lipase activity[10].

High-cholesterol diet The changes in lifestyle habits are the main cause of Hyperlipidemia in which risk factor is mainly poor diet, i.e. greater than 40 percent of total calories of fat, greater than 10 percent of total calories from saturated fat; and greater than 300 milligrams per day of cholesterol intake. Lifestyle contributors include obesity, not exercising, and smoking. Other factors include diabetes, kidney disease, pregnancy, and an underactive thyroid gland[22-23]. Hyperlipidemia at development of hyperlipidemia, atherosclerosis[11].

The main aim of treatment is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular disease. Medicinal plants are used for various research purposes. More than thirteen thousand plants have been studied for various pharmacological properties. An herbal treatment for hypercholesterolemia has no side effects and is relatively cheap, locally available[12-13].

Mentha arvensis, belonging to the family of the Lamiaceae, is a small to moderate sized perennial herb, commonly known as patina, corn mint or wild mint in Bangladesh and India. It is widely cultivated in Bangladesh, Nepal, India, Srilanka, Thailand, and Japan for its use as a food seasoner, household remedy, and industrial purposes. The plant has been reported to possess a large number of different chemicals like α-menthol, neomenthol, menthofuran, d-menthone, isomenthol, isomnethone, menthylacetate, cineol, phellandrene, p-cymene, aromadendrene, limousine, piperitone, carvomenthone, pinene, carvacrol, α-pinene, α-phellandrene, dipentene, cadinene, thujone, menthofuran, caravan, linalool, linalyl acetate and piperitenone oxide, which are used in pharmaceutical, food, flavour, cosmetics, beverages and allied industries[14-17]. The plant leaf and oil contain acetaldehyde, amyl alcohol, methyl esters, limonene, β-pinene, β-phellandrene, cadinene, dimethyl sulphide, and traces of α-pinene, sabinene, terpinolene, transocimene, g-terpinene, fence, α-thujone, β-thujone, citronellol and luteolin-7-O-rutinoside[18]. It also possesses the.[15] According to several reports, the plant contains 90% mint oil. It contains monoterpenes (menthone, menthofuran, methyl acetate cineole and limonene), sesquiterpenes (viridiflorol), flavonoids (luteolin, menthoside, isorhoifolin, routing hesperidin), phenolic acids (caffeic acid, chlorogenic and rosmarinic), triterpenes (Squalene, a-amyrin, urosolic acid and sitosterol), phytol, tocopherols, carotenoids, choline, betaine, cyclones, rosmarinic acid, tannin and minerals[19-21]. More recently, linarin (acacetin-7-O-β-D-rutinoside) was extracted from the flower of the plant.[19]

SYMPTOMS

Generally, hyperlipidemia does not have any noticeable symptoms but it is usually discovered during routine examination or until it reaches the dangerous stage of a stroke or heart attack. The deposits of cholesterol (known as Xanthomas) may form under the skin (especially around the eyes or along the Achilles tendon) in individuals with familial forms of the disorder or in those with very high levels of cholesterol in the blood. Individuals with hypertriglyceridemia may develop numerous pimple-like lesions across their body and usually have a body mass index greater than 30 kg/m2, or waist size greater[24-25].

Diagnosis of hyperlipidemia [26]

As hyperlipidemia doesn't have any visible symptoms in early stages so we should get a blood test for the sake of prevention at regular intervals. The National Cholesterol Education Program recommends that people get this test every 5 years after age 20. The more risk factors for heart

Table I: Serum lipid profile/total protein in male albino Wistar rats (Chronic Model)

Groups	TC (mg/dl)	TP (mg/dl)	TG(mg/dl)	HDL(mg/dl)	VLDL(mg/dl)	LDL(mg/dl)
Normal	78.92±3.12	4.05±0.07	76.92±3.12	38.50±2.029	15.78±0.62	24.60±3.51
High cholesterol Diet	195.7±15.90###	1.923±0.33###	125.8±5.24###	23.12±2.09###	25.14±1.04###	143.4±20.95###
High cholesterol diet+200mg/kg Extract	115.2±10.72*	3.422±0.69***	115.4±5.13**	31.1±1.72***	23.07±1.01**	121.0±9.91*
High cholesterol diet+400mg/kg Extract	98.2±7.67***	4.188±0.34***	110.2±5.00***	36.55±1.38***	22.04±1.06***	96.48±9.70***
High cholesterol diet +Nicotinic acid 100mg/kg	92..9±13.5***	3.865±0.97***	109.1±4.19***	37.28±3.33***	21.83±0.84***	85.69±14.54***

Table II: Serum lipid profile and total protein in male albino Wistar rats (Acute model)

Groups	TC(mg/dl)	TP(g/dl)	TG(mg/dl)	HDL (mg/dl)	VLDL(mg/dl)	LDL (mg/dl)
Normal	93.7±4.81	4.399±0.746	83.97±9.46	40.13±3.14	16.74±1.89	36.84±1.22
Triton	125.0±10.15###	2.205±0.386###	124.0±25.03###	22.66±2.34###	24.8±1.46###	77.54±4.56###
Triton+ 200mg/kg Extract	113.9±5.94*	3.350±0.69*	105.9±6.52ns	31.75±2.18***	21.88±2.3**	60.67±5.78**
Triton+ 400mg/kg Extract	104.4±6.61***	4.330±0.47***	98.46±4.19*	35.73±1.26***	19.69±3.65***	46.98±4.84***
Triton +Nicotinic acid 100mg/kg	100.6±1.12***	4.590±0.58***	99.53±4.85*	37.77±1.65***	19.90±3.67***	42.92±4.87***

All values are expressed as mean ± SEM for six animals in each group using one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparison tests.
Compared with disease control: #P<0.05, ##P<0.001, ###P<0.0001
*Compared with normal control: *P<0.05, **P<0.001, ***P<0.0001*

disease you have, the more aggressively your physician will treat hyperlipidemia. Most blood tests measure levels of LDL (sometimes called "bad") cholesterol, HDL (sometimes called "good") cholesterol, total cholesterol (LDL plus HDL), and triglycerides.

Diet recommendation for hyperlipidemia

Physicians usually recommend making changes in regular diet intake and suggesting exercise habits called therapeutic lifestyle changes (TLC). TLC can lower total cholesterol by 10 to 20 percent in some people. More commonly, there is a reduction of 2 to 6 percent of hyperlipidemia in some people from TLC. A major part of TLC is changing diet of people. The Physician may recommend changes such as:

- Reducing your saturated fat intake to 7 percent of your daily calories;

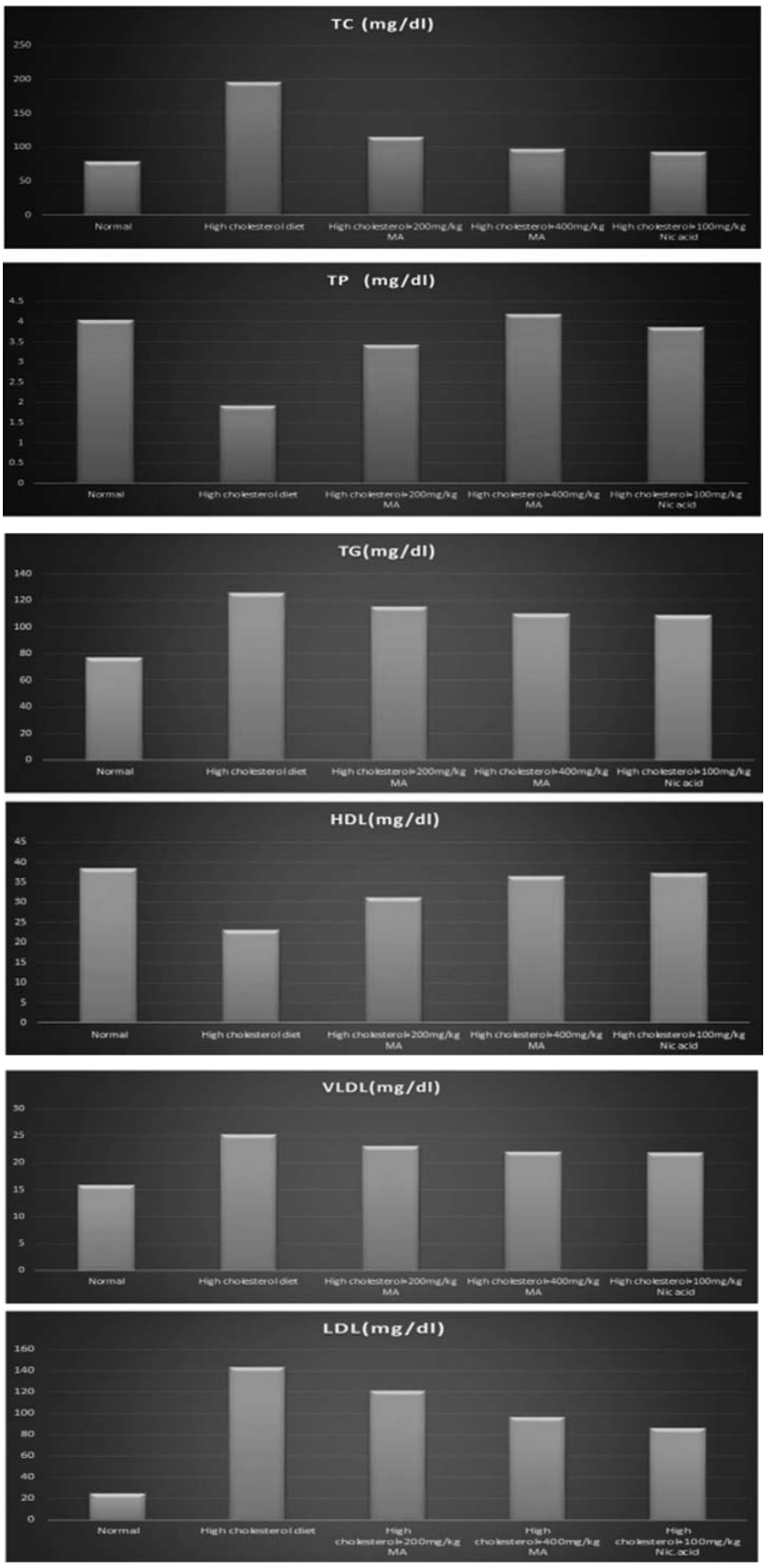

Fig. 1: Effect on TC, TP, TG, HDL, VLDL & LDL in chronic model

- Reducing your total fat intake to 25 to 35 percent of your daily calories;
- Limiting your dietary intake cholesterol to less than 200 mg per day;
- Eating 20 to 30 g a day of soluble fiber, which is found in oats, peas, beans, and certain fruits.
- Recommended increasing an intake of plant sterols, substances found in nuts, vegetable Oils, corn and rice, to 2 to 3 g daily.

Other foods recommended that can help to control cholesterol includes cold-water fish, such as mackerel, sardines, and salmon. Omega-3 fatty acids are present in these fish that may lower triglycerides. Soybeans found in tofu, soya nuts and many meat substitutes contain a powerful antioxidant that can lower LDL. A supplement (psyllium) can help you increase the soluble fiber intake. It is made from seed grain husks. HDL cholesterol level is high if the person is having more weight according to body mass index, and losing of an excess weight can lower your LDL cholesterol levels and increases HDL Cholesterol level [26-27].

MATERIAL AND METHODS

TritonWR-1339, nicotinic acid and cholesterol were purchased from sigma-aldrich and triglyceride kit, cholesterol kit, hdl/cholesterol kit, total protein kit, were purchased from Erba Diagnostic.

Phytochemical screening

Preliminary phytochemical study was carried out to determine the presence of tannins, flavonoids, steroids, saponins, cardiac glycosides, terpenoids, phlobatannins, alkaloids, triterpenoids, anthroquinones and carbohydrate, with various plant extracts[28].

Preparation of extract of *Mentha arvensis*

The plant (fresh leafs) *Mentha arvensis* was collected in the month of August and

September from Dharwad District of Karnataka. The plants were authenticated and identified by experts of Regional Medical Research Centre Belagavi (ICMR). The voucher specimen RMRC-542(ICMR) was deposited at Belagavi, Karnataka India. The plant material was dried in shade, powdered and passed through the sieve course (10/40). The powder was then extracted in Soxhlet extractor, defatted with petroleum ether (40-60 V/V) and extracted with ethanol. The extraction was continued unless the solvent in the thimble was clear; later on the solvent was concentrated in rotary evaporator and stored in refrigerator[29].

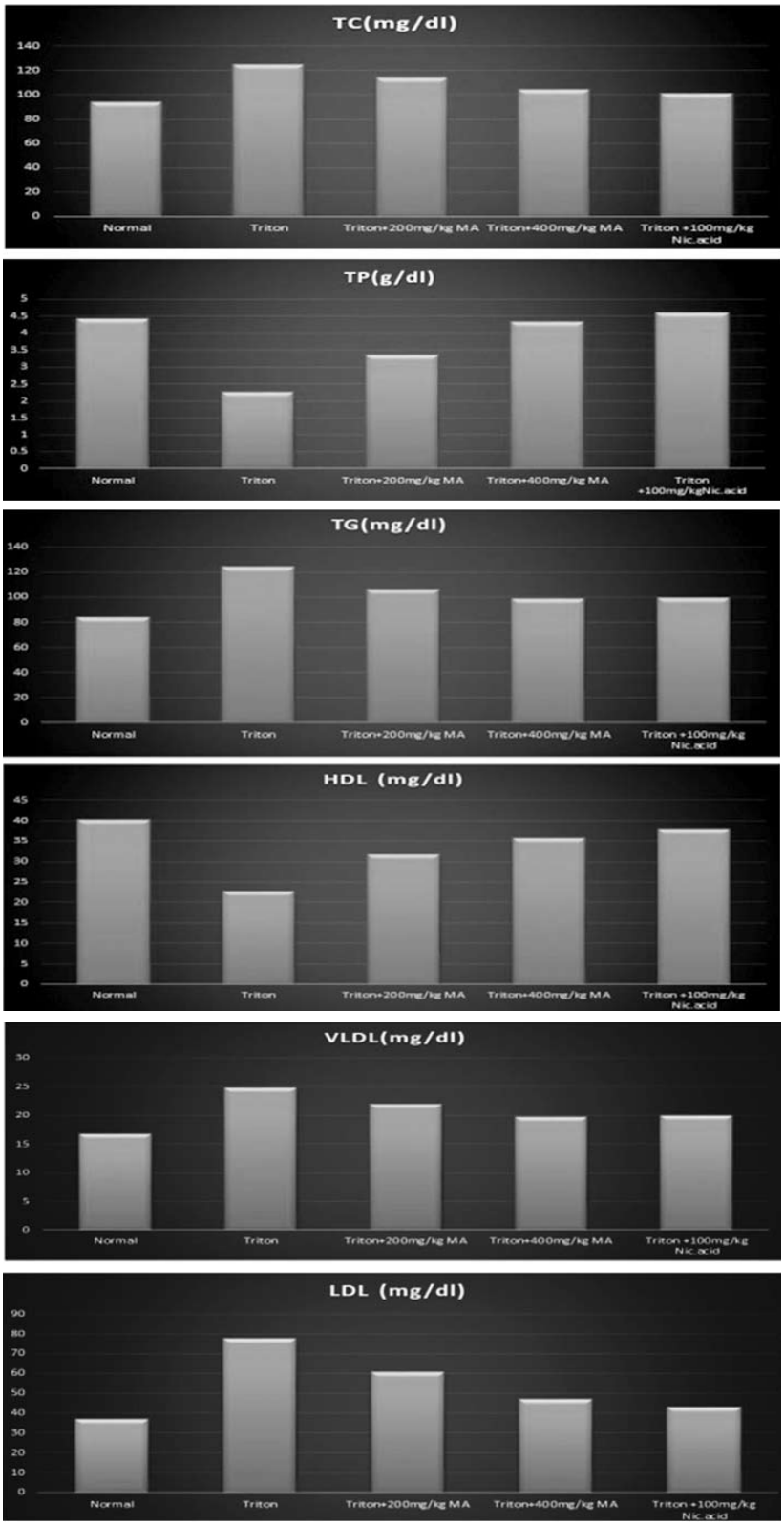

Fig. 2: Effect on TC, TP, TG, HDL, VLDL & LDL in acute model

Animals

The complete study was carried out using 60 healthy male Wistar rats weighing between 180-220g which was procured from Sri Venkateshwara Enterprises Bangalore. They were housed in standard laboratory conditions at room temperature along with light and dark (12:12 h). The animals were provided with standard pellet diet water and *ad libitum*. After seven days of acclimatization period, they were randomly selected and segregated into different experimental groups. Ethical clearances were obtained from institutional ethics committee (IAEC Reg No: 221/CPCSEA) KLEU's college of Pharmacy, Belagavi.

Acute oral toxicity

Acute toxicity studies revealed that EEMA did not showed any significant toxic signs or mortality up to 1000mg/kg, therefore 1/10th and 1/20th dose; i.e. 200mg/kg and 400mg/kg p.o was selected as daily dose and given by oral route for 14 days. The dose of next animal was determined as per OECD guideline 425.

Induction of hyperlipidemia in experimental animals

Hyperlipidemia was induced in overnight fasted rats by Triton WR 1339 (200 mg/kg i.p.) and rats were screened after 72 hours. There will be a significant increase in TC, TG, LDL, VLDL and a decrease in HDL level, but in case of chronic model, hyperlipidemia was induced by feeding with high cholesterol diet for a period of 10 days. All the animals were allowed free access to water and pellet diet and maintained at room temp in plastic cages[10-11].

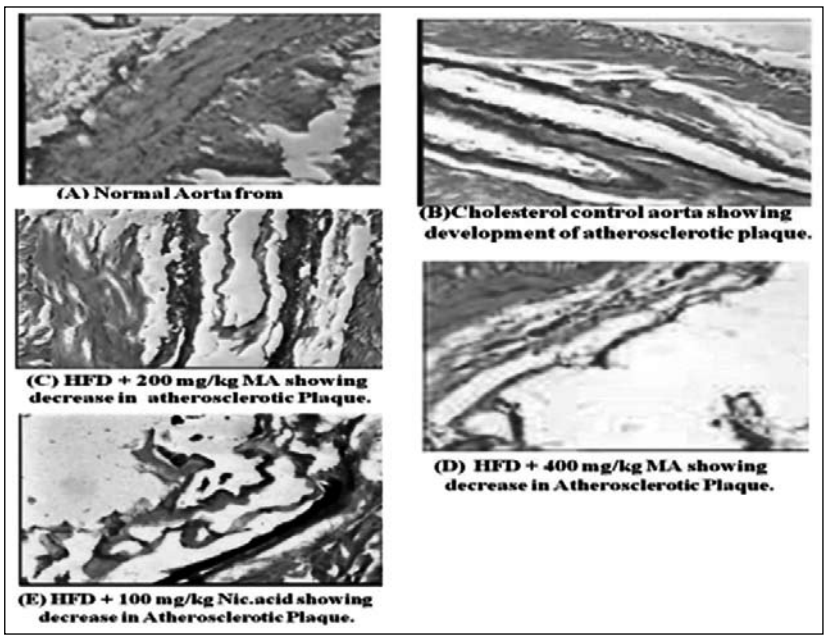

Fig. 3: (A) Normal (B) Induced & (C) (D)(E) showing decrease in atherosclerotic plaque

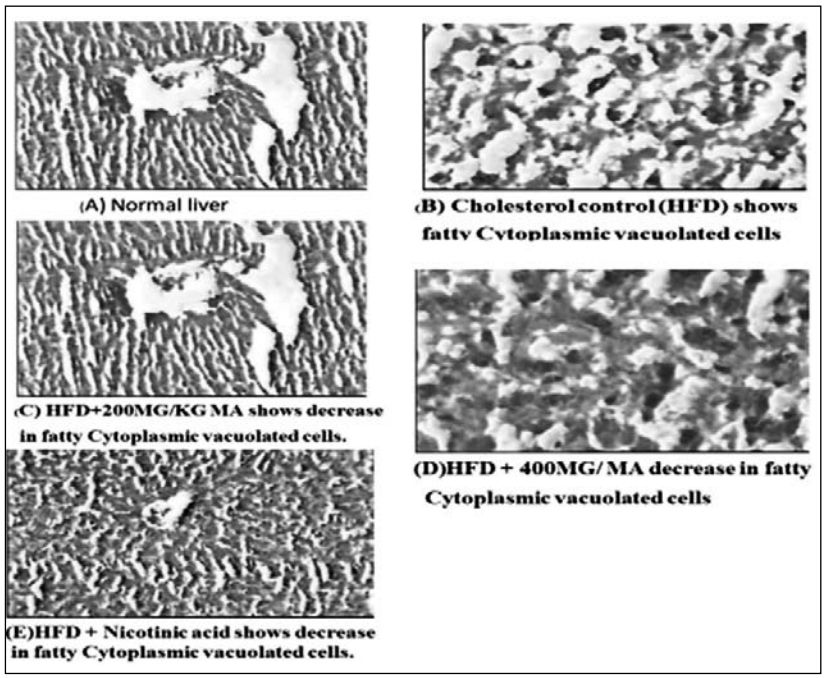

Fig. 4: (A) Normal, (B) Induced & (C)(D)(E) showing decrease in fatty cytoplasmic vacuolated cells

Experimental design

The complete course of experiments was carried out using 60 healthy male Wistar rats [including both (acute 30 animals) & (chronic 30 animals)] weighing between 180-220g and divided into five groups of six rats each. Group I: normal untreated rats; Group II: hyperlipidemic control rats (Triton WR 1339 in acute) & (high cholesterol diet in chronic); Group III: hyperlipidemic rats given EEMA 200 mg/kg body weight in 0.5% of CMC; Group IV: hyperlipidemic rats given EEMA 400 mg/kg body weight in 0.5% of CMC; Group V: hyperlipidemic rats given standard drug Nicotinic acid 100 mg/kg body weight in 0.5% of CMC in both acute and chronic group. On day 3, blood was collected from the retro-orbital plexus of all animals and the serum was separated and stored at 20°C until further use. The animals were sacrificed at the end of experimental period of 14 day by decapitation. Blood was collected and serum was separated by centrifugation at 3000 rpm for 10 min[31-32].

Measurement of biochemical parameters

The amount of Total cholesterol (TC)[33], High density lipoprotein triglyceride (HDL) [33], Triglyceride (TG)[34], was measured by using ERBA Diagnostic Kits. Low-density Lipoprotein (LDL) and Very Low-density Lipoprotein (VLDL) were measured by using Friedewald's formula[35].

VLDL Cholesterol (mg/dl) = TG ÷ 5 and LDL Cholesterol (mg/dl) = TC – (HDL+VLDL).

Histopathological investigation

In histopathological studies, animals were sacrificed. The whole liver and aorta were fixed in formalin (10%) and subjected to histopathological studies. The sections of liver and aorta were processed and embedded in paraffin wax. A section of about 4-6 µm was made and stained with hematoxylin and eosin and photographed[36].

Statistical analysis

All the data expressed as mean ±SEM were evaluated by one-way analysis of variance (ANOVA) followed by Dennett's test for multiple comparisons using prism Graph Pad version 5.0 and values of P0.05 were considered as statistically significant.

RESULTS

Effect on serum lipid profile

Triton and high cholesterol treated group showed

significant increase (P<0.0001) in the levels of TC, TG, LDL&VLDL compared to normal group. Post-treatment with extract *of Mentha arvensis* leaves at different doses (200mg/kg, 400mg/kg), significantly (P<0.001) prevented the elevation of these parameters when compared to hyperlipidemic rats. The results are depicted in Table I.

Effect on Total cholesterol: Post-treatment with 200 mg/kg of extract reduced the serum total cholesterol significantly (P<0.001), but at higher dose of 400 mg/kg it reduces the serum total cholesterol significantly (P<0.0001) in chronic model. In acute model at a dose of 200 and 400 mg/kg, it reduces serum total cholesterol significantly(P<0.0001) and standard group nicotinic acid showed significant reduction in total cholesterol in acute and chronic model when compared to hyperlipidemic rats.

Effect on Triglyceride: Post-treatment with 200mg/kg of extract reduced the serum triglyceride significantly (P<0.001), but at doses 400mg/kg it reduces significantly (P<0.0001) in chronic model. In acute model at dose200and400mg/kg it reduces serum triglyceride significantly at(P<0.0001) and standard group nicotinic acid showed significant reduction in triglyceride in acute and chronic model when compared to hyperlipidemic rats.

Effect on HDL: Post-treatment with 200mg/kg and 400mg/kg of EEMA, increases significantly serum HDL(P<0.0001) in chronic and acute model and standard group nicotinic acid shows significant increase in HDL in acute and chronic model when compared to hyperlipidemic rats.

Effect on VLDL: Post-treatment with 200mg/kg of EEMA reduced the serum VLDL significantly (P<0.001), but at doses 400mg/kg it reduced more significantly (P<0.0001) in chronic model. In acute model at dose 200 mg/kg and 400 mg/kg it reduced serum VLDL significantly (P<0.0001) and standard group nicotinic acid showed significant reduction in VLDL in acute and chronic model when compared to hyperlipidemic rats.

Effect on LDL: Post-treatment with 200mg/kg of EEMA reduced the serum LDL significantly where(P<0.001), but at doses 400mg/kg it reduced significantly (P<0.0001) in chronic model.

In acute model at dose 200 mg/kg and 400 mg/kg it reduces serum LDL significantly (P<0.0001) and standard group nicotinic acid showed significant reduction in LDL in acute and chronic model when compared to hyperlipidemic rats. In hyperlipidemic rats there is significant increase in TC, TG, LDL, VLDL level and significant decrease in HDL level, but after Post treatment with EEMA, there is significant decrease in TC, TG, LDL, VLDL and increase in HDL level.

HISTOPATHOLOGY STUDY

Histopathology of aorta

In the histopathological study high cholesterol diet fed rats exhibit atheromatous plaque as compared to normal control in aorta where as in case of liver high cholesterol diet fed rats shows fatty cytoplasmic vacuolated cells in comparison with normal control.

Histopathology of liver

In the histopathological study high cholesterol diet fed rats shows fatty cytoplasmic vacuolated cells as compared to normal control. Treatment with EEMA shows less fatty cytoplasmic vacuoles as compared to high cholesterol diet fed rats.

DISCUSSION

Ethanolic extract of *Mentha arvensis* is non–toxic up to the dose of 2000 mg/kg and did not cause any death of the tested animals. The results are discussed under the lipid profile in serum and in liver. Lipid profile in serum and liver indicates increased phospholipids (PL), triglyceride (TG) and cholesterol levels were significantly reduced by treatment of 100 mg/kg of nicotinic acid. LDL and VLDL levels were significantly increased in Triton-injected animals to control rats.

High cholesterol diet increased serum cholesterol and LDL-C level significantly. A rise in LDL may cause deposition of cholesterol in arteries and aorta and hence it is a direct risk factor for coronary heart disease. Studies show that both LDL and VLDL have a positive role in atherogenesis.

Triton WR 1339 has been widely used to block clearance of triglyceride-rich lipoproteins to induce acute hyperlipidemia in several animals[30]. This model is widely used for a number of different aims particularly; in rats it has been used for screening natural or chemical hypolipidemic drugs. Ethanolic extracts of *Mentha arvensis* leaves tested in the present study significantly prevented hyperlipidemia.

Triton and high cholesterol diet induced hyperlipidemia is associated with increased levels of lipids in the serum.

Table III: Serum lipid profile/total protein in male albino Wistar rats (Chronic Model)

Groups	TC (mg/dl)	TP (mg/dl)	TG(mg/dl)	HDL(mg/dl)	VLDL(mg/dl)	LDL(mg/dl)
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High cholesterol diet +Nic. acid 100mg/kg	92..9±13.5***	3.865±0.97***	109.1±4.19***	37.28±3.33***	21.83±0.84***	85.69±14.54***

All values are expressed as mean ± SEM for six animals in each group using one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparison tests.

Compared with disease control: #P<0.05, ##P<0.001, ###P<0.0001

*Compared with normal control: *P<0.05, **P<0.001, ***P<0.0001*

Increased levels of total cholesterol, TGs, HDL, LDL and VLDL in the Triton and high cholesterol treated group indicate that Triton and high cholesterol may interfere with metabolism or biosynthesis of lipids.

Phytochemical investigation has shown the presence of saponins and phenolic compounds in the ethanolic extract of *Mentha arvensis*. Observed hypolipidemic activity of all the doses could be attributed to the saponins since saponins have been reported to possess hypolipidemic activity. Triton and high cholesterol diet induced hyperlipidemia is associated with lowered levels of proteins in the serum. Lowered levels of proteins in the Triton and high cholesterol treated group indicate Triton and high cholesterol may interfere with metabolism or biosynthesis of lipids. Histopathological examination of liver and aorta in normal group showed normal integrity of the liver and aorta cell membrane. No inflammatory cells infiltration was seen in the rat heart of normal group. In triton and high cholesterol induced group, shows changes in the liver and aorta.

In the aorta there is development of atherosclerotic plaque whereas in liver there is an increase influx of free fatty acids observed. Post treatment with *Mentha arvensis* at different doses 200 mg/kg and 400 mg/kg showed reversal of atherosclerotic plaque and influx of free fatty acids to normal. The results presented in this study indicate that the ethanolic extract of *Mentha arvensis* leaves at doses 200 mg/kg & 400 mg/kg after 14 days' administration decreases in Triton and high cholesterol diet induced increased levels of total cholesterol, TGs, LDL, VLDL, and HDL. Among the doses, 400 mg/kg decreases the lipid parameters more significantly than the 200 mg/kg indicating higher dose is more protective than the lower dose.

CONCLUSION

The present study suggests that post-treatment with ethanolic extract of *Mentha arvensis* leaf showed dose dependent antihyperlipidemic action against Triton and High cholesterol diet induced hyperlipidemia. The overall antihyperlipidemic action of ethanolic extract of *Mentha arvensis* leaf is probably due to its antioxidant and free radical scavenging activity. Pretreatment with *Mentha arvensis* at doses 200 mg/kg and 400 mg/kg significantly restored all the biomarker enzymes in serum induced by Titon and high diet cholesterol.

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