ISSN- 2230-7346

Journal of Global Trends in Pharmaceutical Sciences

RAMIFICATION OF HYDROALCHOLIC EXTRACT OF MIMSOPS ELENGI ON TRITON INDUCED ATHEROSCLEROSIS RATS

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ARTICLE INFO

Key words:

Mimusops elengi Triton WR-1339, atorvastatin, atherosclerosis

Access this article online Website: https://www.jgtps.com/ Quick Response Code:

ABSTRACT

Mimusops elengi is populary known as bakul,magilam poo belongs to Sapotaceace found in tropical forest in South Asia and Northern Australia. The tribes of Malayali and Muthuvan of Kerala, Kalrayan and Kani of Tamilnadu used the leaf and its preparation is used for tooth ache, uterus problem and mouth freshner, bleeding gum for body shine respectively. The phytochemical review of leaf, flower, fruit, seed and the whole plant revealed the presence alkaloid carbohydrate, sterols, terpenoids, flavonoids, volatile oil.Pharmacological review of leaf exhibited lipid peroxidation effect, wound healing & immunopharmacological activity. Literature survey revealed the preliminary phytochemical studies for the leaves was not so far. An endeavour was taken to investigate the protective effect of this plant extract in triton L-induced atherosclerosis in rats. The aim of the present study is to evaluate the effect of hydroalcoholic extract of Mimusops elengi on Triton induced HDL-induced atherosclerosis in Wistar rats (200-220g). Serum samples are analyzed for its biochemical estimation. Rats were sacrificed and blood samples were withdrawn from the retro orbital venous plexus. Superoxide dismutase, catalase,Gluthathione reductase and lipidperoxidation levels were determined from the heart homogenate. Liver and carotid artery were isolated and subjected to histopathological studies. Group which received herbal concoctions showed reduced in serum total cholesterol, High density lipoprotein, triglycerides, level low density lipoprotein, very low density lipoprotein and athrogenic index were determined in comparision with atorvastatin. Increased antioxidant and prooxidant level were estimated. Mimusops elengi showed significant and mild protective effective against Triton WR induced atherosclerosis in a dose dependent manner when compared with atorvastatin.

INTRODUCTION

Atherosclerosis with its clinical manifestation such as ischaemic heart disease stroke peripheral arterial disease is leading vascular disease the lumen in situ or embolize to occlude distal narrow lumen clinical investigation of atherosclerosis resulted that degree of stenosis caused by plaque [1] . Modern medicine causes adverse effects such as cold symptoms or stuffy nose, diarrhoea, joint pain, urinary tract infection, nausea, loss of appetite, indigestion, stomach discomfort or pain, increased transaminases, muscle spasms with or without pain[2]. It is essential and immediatetoide ntifythealternativetherapyand usage. *Mimusops elengi* is popularly known as magilampoo, bakul belongs toSapotoceace found in places throughout India & Pakistan, especially in Eastern Ghats, Western Ghats and Central Deccan plateau area where frequently cultivated in gardens [3-4]. The tribes of Malayali and Muthuvan of Kerala, Kalrayan and Kani of Tamilnadu used the leaf and its preparation are used for toothache, uterus problem and mouth freshner, bleeding gum,and for body shine respectively [5-12]. Phytochemical review of leaf, flower, fruit, seed and the whole plant revealed the

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presence of alkaloid carbohydrate, sterols, terpenoids, flavonoids, volatile oil [13-14]. Pharmacological review of leaf exhibited lipid peroxidation effect,wound healing& immuno pharmacological activity[15-17]. An endeavour was taken to investigate the protective effect of this plant extract in HDL-induced atherosclerosis inrats.

MATERIALS AND METHODS

Collection of plant materials

Leaves were collected from Meenakshi Mission Hospital campus in Madurai, Tamil Nadu in the month of January 2020. The species for the proposed study was identified and authenticated by DR. Stephen, Professor ,Department of Botany , American college Madurai- 625002.The herbarium of this specimen was kept in the department for further reference.

Preparation of plant material

The leaves were collected dried in shade coarsely powdered passed through sieve no 40 and stored in closed container for further use .All reagents were used of analytical grade.

Preparation of Hydro-alcoholic extract of *Mimusops elengi* (HAEME)

Theleaveswerecollected,shadedriedandcoarselypowdered,passedthroughsieveno 40, was extracted with 70% hydroalcohol by maceration technique was concentrated to drynesss and stored in a closed container for further use. Hydro ethanolic extract of*Mimuspos elengi* linn (HAME) were dissolved in distilled water and administered as such at the dose of 2000 mg/kg bodyweight.

Acute toxicity studies

According to OECD-423 guidelines acute oral toxicity was carried out in different animalswithvariousdoses[18].Eachgroupreceived theconcoctionatdoses50,300,1000and 2000 mg/kg and observed for about 24 hours continuously to detect behavioral, neurological and autonomic parameters. No lethality was found inanimals.[18]

Experimental animals

Healthy young adult female animal of Wistar rats (*Rattus norvegicus)* between 8-12 weeks old were used for the studies. The experiment was conducted after the approval by the Institutional Animal Ethical Committee, Central Animal House, Pallavan College of Pharmacy, Iyyengarkulam, Kanchipuram (165/PO/a/18/CPCSEA Pro.No:PCP/IACE/2020, dt 09.2020). Organization of Economic Co-operation and Development (OECD) Guidelines for the testing of Chemicals Acute Oral Toxicity-Up-and-Down.

Experimental protocol

Animals were divided into different groups of six rats each (n=6).

Group-INormal control

Group-II Triton WR-1339 in normal saline(disease received) for 14 days . Group-III received Atorvastatin (1mg/kg b.w oral)

Group-IV HAEME extract (200 mg/kg b.w) concoction was given on 7 days + Triton (15days) Group-V HAEME extract (400 mg/kg b.w) + Triton(15days)

Same protocol was followed for 14 days also. Blood samples were withdrawn from the retro orbital venous plexus of rats. Serum was seperated and analyzed for biochemical estimation of lipid parameters and in vivo antioxidant levels were determined.

BIOCHEMICAL ANALYSIS

Determination of serum Lipid profile

Serum levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), were determined by using the kit of Agappe Diagnostic Ltd., India. Activities of these serum parameters were measured using semi autoanalyzer (RMS, India). Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C),athrogenic index were calculated as per the standard methods[19]

DETERMINATION OF TISSUE ANTIOXIDANT LEVEL

Assay of superoxide dismutase (SOD)

The method was adopted as per method (Kakkar et al .,1984) [20]

Procedure

0.5 ml of the sample (tissue homogenate) was diluted to 1 ml with ice cold water. 2.4 ml of ethanol and 1.5 ml of chloroform (in chilled condition) were added. The mixture was shaken for 1minute for 40C and then centrifuged. The enzyme activity in the supernatant was determined. The assay mixture contained 1.2 ml sodium pyrophosphate buffer, 0.1 ml phenazine methosulphate, 0.3 ml of nitroblue tetrazolium, appropriately diluted enzyme preparation and water ina total volume of 3.0ml.The reaction was started by the addition of 0.2 ml NADH. After incubation at 300C for 90 seconds, the reaction was stopped by the addition of 1.0ml of glacialacetic acid. The

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reaction mixture was stirred vigorously and shaken with 4.0 ml of n-butanol. The mixture was allowed to stand for 10 minutes and then centrifuged. The colour intensity of the chromophore in butanol layer was measured at 560nm against butanol blank and a system devoid of enzyme served a control. One unit of enzyme activity was defined as the enzyme reaction which gave 50% inhibition of NBT reduction in one minute under the assay condition and the activity were expressed as units/mg protein. The results are displayed in the following table 3 and fig3

Assay of Catalase : The method was adopted as per method (Sinha,1972) [21]

Procedure

To 6.0 ml phosphate buffer, 0.1 ml sample and 0.4 ml hydrogen peroxide were added. The reaction was stopped at 15, 30, 45 and 60 seconds by the addition of 2ml of dichromate-acid reagent. The tubes were kept in boiling water for 10 minutes and the colour developed was read at 620 nm. Standard in the range of 2-10 _M were taken and proceed similar to the test with blank containing reagent alone. The activities were expressed as _M of hydrogen peroxide consumed/minute/ mg protein. The results are displayed in the following table 4 and fig 4.

Assay of glutathione peroxidase: The method was adopted as per method(Rotrucket al.,1973)[22]

Procedure

To 0.2 ml of tris buffer, 0.2 ml EDTA, 0.1 ml sodium azide, 0.5 ml sample (tissue homogenate) and 0.2 ml GSH were added followed by 0.1 ml hydrogen peroxide. The contents were mixed well and incubated at 37oC for 10 minutes along with the tube containing the entire reagent except the sample. After 10minutes,there action was arrested. by the addition of 0.5 ml of `0% TCA, centrifuged and the supernatant was assayed for GSH. The results are displayed in the following table 5 and fig 5.

Assay of glutathione reductase : The method was adopted as method (David et al .,1983)[23]

Procedure

The assay system contained 1 ml of 0.12M potassium phosphate buffer, 0.1ml of 15 mM EDTA, 0.1 ml of 10 mM sodium azide, 0.1 ml of 6.3 mM oxidizedglutathione and 0.1ml of enzyme source and water in a final volume of 2 ml, keptfor 3 min. Then 0.1 ml of NADPH19 was added. The absorbance at 340 nm wasrecorded at an interval of 15 sec for 2-3 min. for each series of measurement.Control was done that contained water instead of oxidized glutathione.The results were displayed in the following table 6 and fig 6 .

HISTOPATHOLOGICAL CHANGES IN THE LIVER AND ARTERY OF RATS TREATED WITH HYDRO ETHANOLIC EXTRACT OF *MIMUSPOS ELENGI* LINN (HAEME)

Small pieces of sample (Liver or artery) fixed in 10% buffered formalin were processedforembeddinginparaffin.Sections(56 m)werecutandstainedwithhaematoxylin and eosin and examined for histopathological changes under the microscope (Motic AE 21, Germany). The microphotographs were taken using Moticam 1000 camera at original magnification of 100x.The results are displayed in the following figure 7 & table7.

STATISTICAL ANALYSIS

Statistical analysis was carried out by using Prism Graph-Pad Instat statisticalpackage (6.04 versions, 2014 edition USA). Values are expressed as mean±SD. For multiple comparisons, one way ANOVA was used followed by Tukey's test. p<0.05 was consideredas significantanditwasdenotedas*,p<0.01wasconsideredastoosignificantanditwasdenoted as **, p<0.001.

Effect of hydroalcoholic extract on Triton-induced atherosclerosis in rats Hydroalcoholic extract was prepared into concoction by using distilled and was administered at the dose 200mg &400 mg p.o from 8 to15 th day. The effect was observed in rats and its lipid profile were determined. Total cholesterol levels, HDL-Chloesterol level and triglyceride level were determined and presented in table 1 and fig1.

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Table.1 Effect of Herbal concoction on Serum Total cholesterol level, HDL-cholesterol level &Triglyceride level.

Group	Total Cholesterol		HDL-Cholesterollevels (mg/dl)		Triglyceride levels(mg/dl)	
	8th day	15th day	8th day	15th day	8th day	15th day
Normal-	80.97 ± 2.86	75.62±0.18	32.08±0.84	34.98±0.54	102.2±2.88	122.9±1.60
Triton group	147.0±3.76*	146.9±0.38*	12.85±1.19*	19.83±0.53*	160.6±8.85*	171.4±0.80
Standard group	125.8±3.66**	100.25±0.38**	41.74±5.26**	49.10±0.56**	126.4±1.32**	130.7±0.64
Herbal concoction-I	133.3±2.87**	102.3 ± 0.57**	32.87±1.61**	38.57±0.25**	133.0±2.96**	149.8±0.76
Herbal concoction-II	129.5±2.85**	95.82 ± 0.53**	35.23±2.01**	42.38±0.17**	131.2±2.63**	145.0±2.01

mean ± SEM and n=6, *represents

p<0.001 when compared with normal group,represents p<0.001 whencompared with triton group.Herbal concoction prepared from *Mimusopselengi* of dose 200 showed increased in HDL cholesterol level and triglycerides, 400mg showed decreased inHDL-cholesterol level and triglyceride in comparison with trition induced group and atrovasatin.**

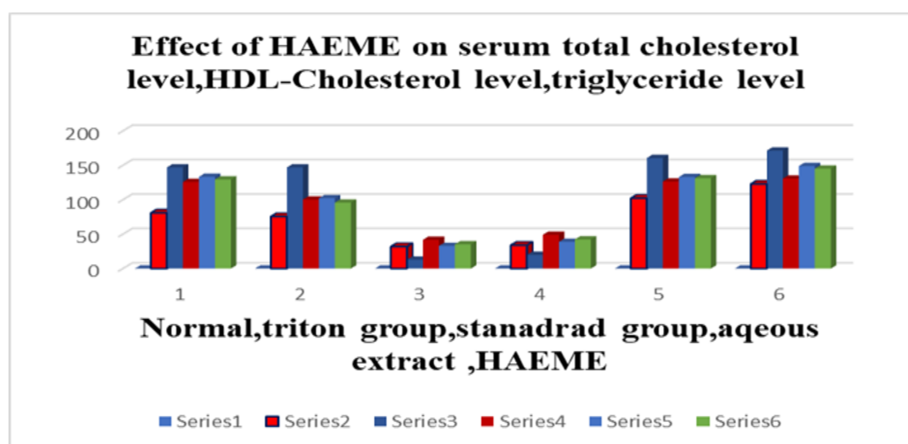

Table 2. Effect of Herbal concoction on serum LDL-Cholerstrol, VLDL levels & Athrogenic index

Groups	LDL-Cholesterol levels (mg/dl)		VLDL levels s(mg/dl)		Athrogenic index	
	8th day	15th day	8th day	15th day	8th day	15th day
Normal	30.45 ±0.89	18.06±0.50	20.44±1.06	22.58±0.79	1.450±0.81	1.161±0.36
Triton group	102.03±1.25*	92.72±0.46*	32.12±1.8	34.28±0.56*	9.685±0.94*	6.407±0.4
Standard group	39.78±1.12**	25.01±0.44**	25.28±0.72**	26.14±0.5**	1.579±1.32**	1.041±0.42**
Herbal concoction-I	63.38±0.97**	33.73±0.44**	26.6 ± 1.08**	29.96±0.54**	2.751±0.92**	1.652±0.39**
Herbal concoction-II	58.03±0.98**	24.44±0.53**	26.24±1.01**	29.0 ± 0.89**	2.391±0.97**	1.260±0.35**

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Representsp<0.001whencomparedwithnormalgrouprepresentsp<0.001whencompared with triton group.Herbal concoction prepared from from *Mimusops elengi* of dose 200mg showed increased athrogenic index and 400mg showed decreased in athrogenic index in comparsion with triton induced group atrovasatin**

Table 3 Effect of Herbal concoction in liver biochemical parameters SOD

Group	**Invivo antioxidant levels**
	Superoxidase dimustase (U/mg protein)
Normal-I	8 ± 0.80
Triton group-II	4.324 ± 0.51*
Standard groupIII	7.648 ± 0.72**
Herbal concoction-IV	8.546 ± 0.72**
Herbal concoction-V	9.848± 0.82**

*representsp<0.001whencomparedwithnormalgroup**representsp<0.001whencompared with triton group

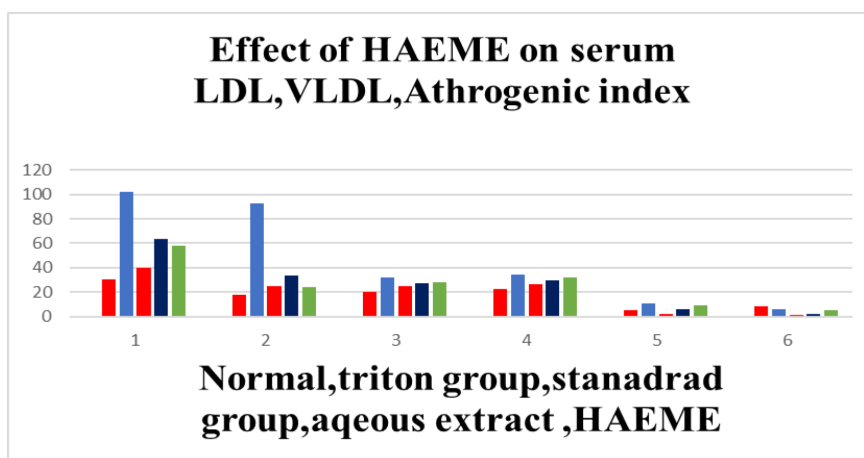

Figure 2.Effect of HAEME on serum LDL,VLDL, Athrogenic index

Figure 3 Effect of Herbal concoction in liver biochemical parametersSOD (U/mg protein)

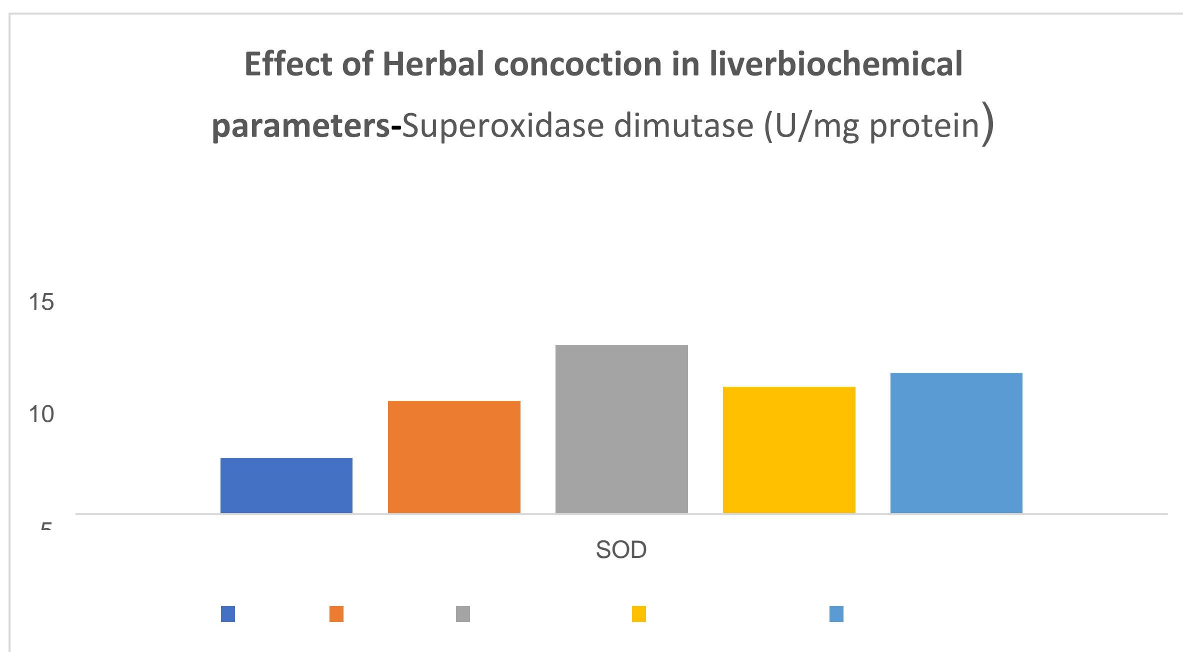

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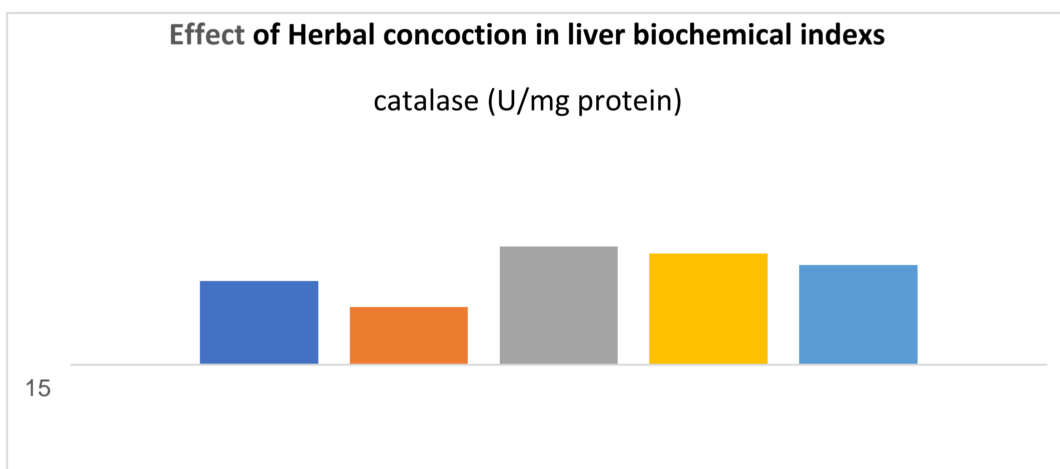
Table 4 Effect of Herbal concoction in liver biochemical parameters Catalase

Groups	Invivo antioxidant levels
	Catalase (μm H2O2 consumed/mg protein)
Normal-I	10.58 ± 0.53
Triton group-II	6.126 ± 0.44*
Standard groupIII	10.74 ± 0.79**
Herbal concoction-IV	10.63 ± 0.87**
Herbal concoction-V	10.59 ±0.63**

*Represents p<0.001 when compared with normal group**represents p<0.001whencompared with triton group.



***In vivo*- Anti-oxidant levels:** Liverhomogenatewaspreparedandwasscreened forinvivoantioxidantlstudiessuch as SOD, catalase, GSH and lipid peroxidation. Herbal concontion prepared from from *Mimusops elengi* in dose of 200 and 400mg showed increased Superoxide dimutase levels.In comparision with triton and standard group. Superoxidase dismutase levels were determined and displayed in table3 and fig 3.

Determination of catalase: Herbal concontion prepared from from *Mimusops elengi* in dose of 200/400mg showed incresed catalase levels in comparison with Triton and atorvastation group.Catalase were determined and displayed in table 4,fig 4

Determination of GSH: Herbal concontion prepared from *Mimusops elengi* in dose of 200& 400mgshowed increased glutathione reductase levels when compared with standard group . GSH results were determined and displayed in table 5 and fig 5

Determination of lipid peroxdation(LPO): Herbal concontion prepared from from *Mimusops elengi* in dose of 200/400mg showed decreased lipid peroxdation levels in comaparision with standard group. LPO results were determined and displayed in table 6 and fig 6

DISCUSSION: Thrombus formation contributes to the development of cardio vascular disease such as atherosclerosis, stroke and hypertension[24-25].Therefore, the inhibition of thrombus formation is important to prevent cardiovascular diseases.HDL-atherosclerosis is induced by Triton WR-1339 ,which accelerates hepatic cholesterol synthesis, physically alters very low density lipoproteins rendering them refractive to the action of lipolytic enzymes of blood and tissues, prevent or delaying their removal from blood[26]. The most commonly used model is ferric chloride injury on carotid artery, triggers vascular wall injury and denudation of endothelium via a mechanism involving the generation of reactive oxygen species[27]. Exposure of collagen triggers platelet activation and exposure of tissue factor activates the coagulation cascade. In the present study $Fecl_3$ (10%) solution dipped in cotton was used to induce carotid artery thrombosis, Group V and IV received herbal concoction(200 and 400mg) prevented the collagen fibre damage in the arterial wall which would triggers the vascular wall injury and denudation of endothelium via a mechanism involving the generation of reactive oxygenspecies.

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Table 5 Effect of Herbal concoction in liver biochemical parameters GSH

Groups	Invivo antioxidant levels
	GSH (µM GSH/mg protein)
Normal-I	9.454 ± 1.00
Triton group-II	5.35 ± 0.64*
Standard groupIII	10.05 ± 0.49**
Herbal concoction-IV	9.516 ± 0.41**
Herbal concoction-V	10.58 ± 0.68**

* represents p<0.001 when compared with normal group **represents p<0.001 when compared with triton group.

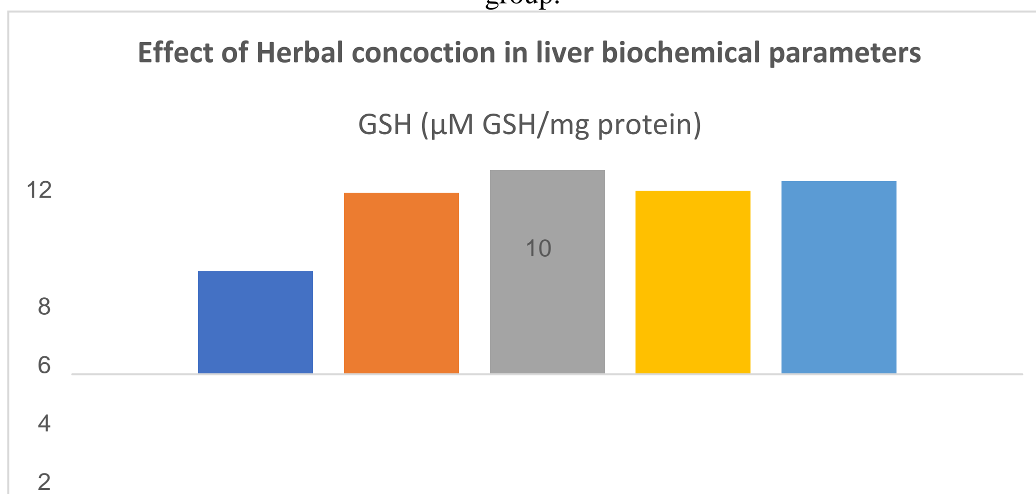

Figure 5 Effect of Herbal concoction in liver biochemical parameters GSH (µm GSH/mg pro)

Table 6 Effect of Herbal concoction in liver biochemical parameters (Pro-oxidant-LPOlevels)

Groups	Pro-oxidant LEVELS
	LPO (Nm of MDA/mg protein)
Normal-I	0.448 ± 0.06
Triton group-II	1.288 ± 0.14*
Standard groupIII	0.453 ± 0.72**
Herbal concoction-IV	0.718 ± 0.05**
Herbal concoction-V	0.492 ± 0.11**

* represents p<0.001 when compared with normal group
**represents p<0.001 when compared with tritongroup.

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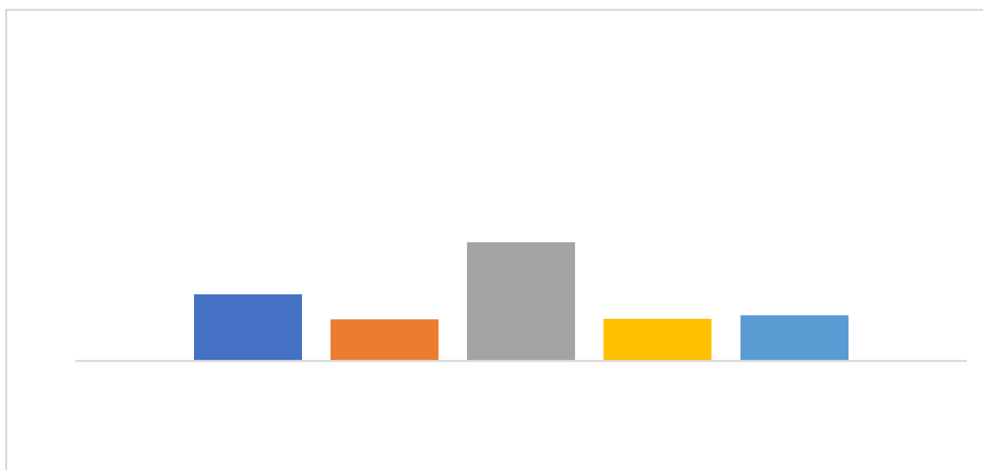
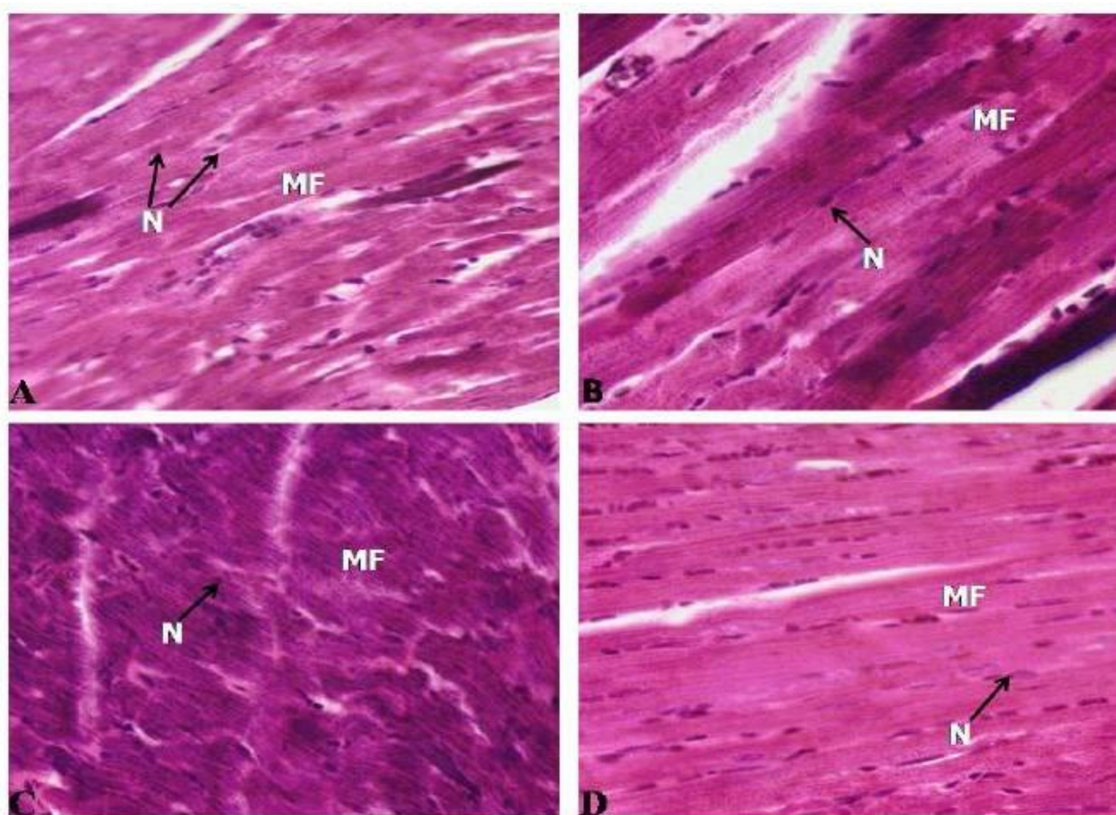


Figure 6 Effect of Herbal concoction in liver biochemical parameters Pro-oxidant - LPO

HISTOPATHOLOGY OF LIVER: The following image describes the myocardial fibrosis has occurred, by the herbal concoction it has been slightly prevented shown in image D



A-(Triton group),B-(Atorvasatatin group),C-Herbal concoction I, D-Herbal concoction II N-Normal MF indicates -Myocaridal fibrosis. Group V and IV received herbal concoction(200 and 400mg) prevented the damage of myocardial fibrosis.

Figure 7: Effect of herbal concoction on histopathology of Liver (10X)

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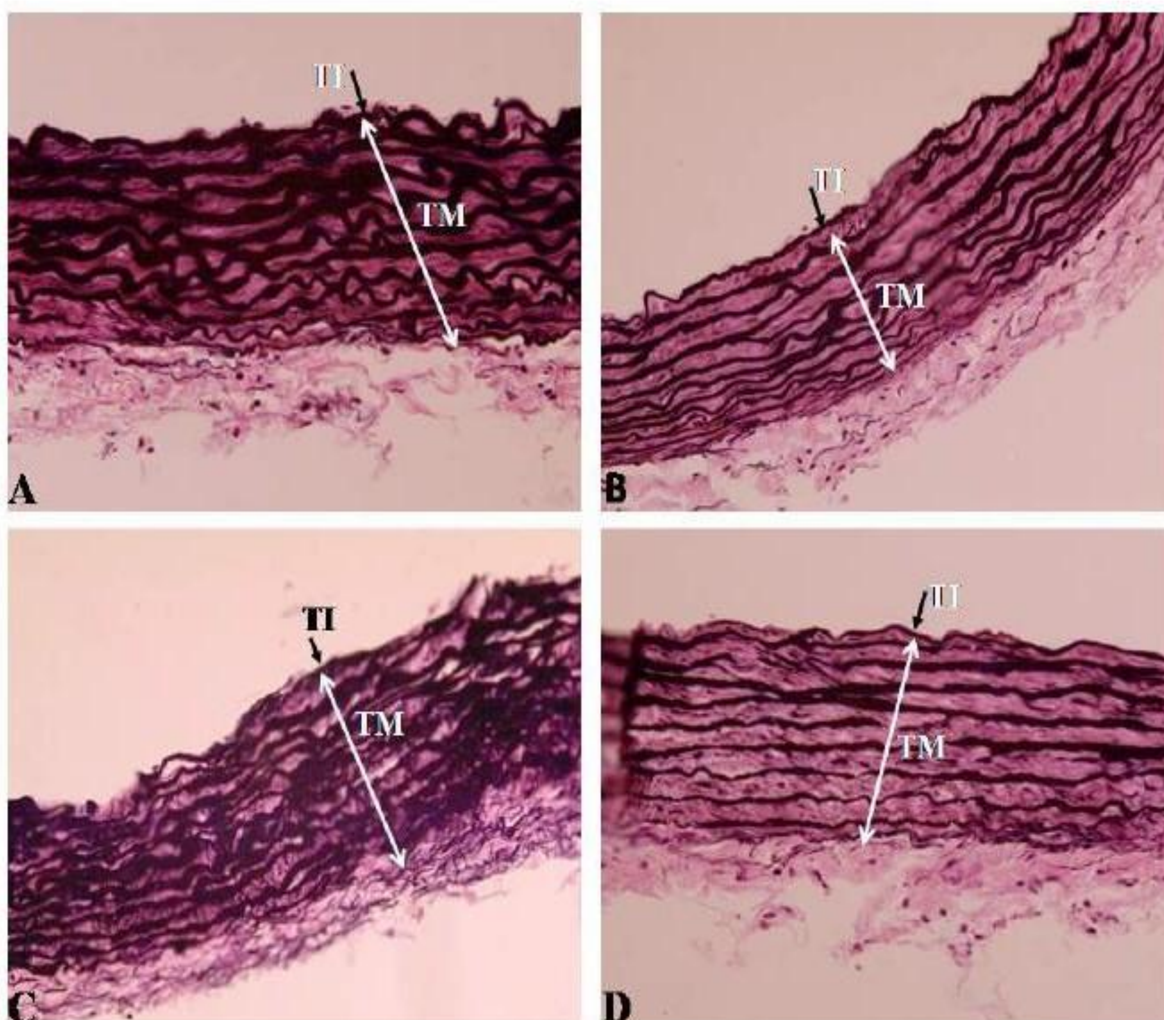

Figure: 8- Photo micrograph of Carotid artery sections (10X)

A-(Triton group),B-(Atorvasatatin group),C-Herbal concoction I, D-Herbal concoction II , TI-Tunica intima, &TM-Tunica media Group V and IV received herbal concoction(200 and 400mg) prevented the collagen fibre damage in the arterial wall which wouldtriggers the vascular wall injury adenudation of endothelium via a mechanism involving the generation of reactive oxygen species.

Antithrombotic effect was evaluated by histological changes observed in the carotid arteries damage in the vessel was found ,which is prevented by herbal concoction& standard drug . Currently available hypolipidemic drugs; statins, fibrates, bile acid sequestraints have been associated with a number of toxic side effects and devoid of antioxidant property [28-29]. In the present study, administration of concoctions in two different doses (200 and 400 mg) significantly reduced serum TG, TC, VLDL and LDL levels and this implies herbal medicine are relatively safe, available, cost-effective bears less or no adverse effect, concoctions have beneficial effects on serum lipid profile by reducing the lipid levels.[30] In histochemical A study, the collagen fiber damage in the vessels induced by Fecl3 was slightly prevented by concoction and standard drug. Hence, in vivo antioxidant results indicated that in Triton control group showed increased levels of LPO and decreased levels of SOD, GSH andcatalase[31]Thisstudyshowedthattheintakeofconcoctionpreparedfrommedicinalplants in rats results in increase in antioxidants and decrease in malondialdehyde which may reduce the risk of inflammatory and heart diseases[32-33]

CONCLUSION

This study revealed that HAEME showed atherosclerosis reversed the effect of triton WR 1399 in rats, in vivo antioxidant effect of hydroalcoholic extract has the

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modulating property of the plant .Hence extensive studies required to explore the extract mechanism responsible for the management of atherosclerosis Further formulation can be developed and can be added as adjuvant therapy in the management of atherosclerosis.

ACKNOWLEDGEMENT

We are grateful to our respectable Dean, Dr.J.Sangumani M.D (General Medicine), Madurai Medical College, Madurai for providing this research facility to carry out this work.

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