Research Article

Safety and Efficacy of *Mukia maderaspatana* Linn in High-Fat Diet Emulsion-Induced Steatohepatitis (NASH) with Fibrosis in Albino Rats

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ABSTRACT

Introduction: NASH forms due to the fat accumulation with inflammation and scarring. The aim and to evaluate the effect of extract of *Mukia maderaspatana* Linn (MM) leaves against High-Fat Diet Emulsion induced steatohepatitis in pre-clinical setting using Albino rats.

Methods: Steatohepatitis (SH) was induced in rats by non-alcoholic high fat emulsion (10 mL/kg, p.o.). Treated the extract of *Mukia maderaspatana* (*M. maderaspatana*) leaves different doses for 12 weeks respectively and standard drug (silymarin) from 5th week onwards. The effect of extract and standard drug on biochemical parameters, such as liver enzymes, total bilirubin, lipid profile and hematological parameters were assessed. Animal weight and intake of food and water were recorded and analyzed.

Results: A significant reduction of lipid profile was observed. The gradually increase in HDL-c level and RBC count were noted, while WBC count was decreased. Histopathological studies confirmed the formation of steatosis, hepatic inflammation, vacuolation and diffuse cytoplasm and hepatocytes. These changes were significantly improved with administration of *M. maderaspatana* leaf extract. In vitro antioxidant studies (DPPH and total antioxidant activity) showed significant reduction in free radicals developed due to the administration of high-fat diet emulsion.

Conclusion: The results of evidenced that the extract of *M. maderaspatana* Linn leaf reduces the steatohepatitis induced by High-Fat diet emulsion.

Keywords: NASH, *M. maderaspatana*, *Mukia maderaspatana*, NAFLD, Steatohepatitis, Fatty liver disease, High fat emulsion.

INTRODUCTION

NAFLD is the most prevalent cause of CLD (chronic liver disease) in humans[1]. The hepatic triglyceride concentration of more than 5% and a simple steatosis histological characteristic, with no signs of alcohol misuse. It is a metabolic syndrome like HDL- Cholesterol, hyperglycemia etc[1].

The effective Non-alcoholic steatohepatitis preventive and treatment options is complicated. Understanding the molecular causes of Non-alcoholic steatohepatitis requires the use of an animal model. Another crucial technique for evaluating the therapeutic efficacy of particular drug against Non-alcoholic steatohepatitis is an *in vivo* NASH model in animals. Animals may develop Non-alcoholic steatohepatitis due to a variety of causes that alter the disposition of hepatic fat. Numerous factors that affect the disposition of hepatic fat can result in the production of NASH in animals.

Definition of "nonalcoholic fatty liver disease" is mostly derived from eliminating alcohol-related histopathology and focusing on what "does not" contribute to fatty liver. This is primarily brought on by information gaps in the understanding of the natural history of NASH, which also present a challenge in formulating a clear strategy of the patients. The disagreement over whether Non-alcoholic fatty liver disease should be counted among diabetes-related co morbidities is another issue that is unlikely to be settled without mechanistic investigation that assesses the connection between the two illnesses. It is also necessary to talk about how to diagnose NAFLD when diabetes (type-2) already exists. Although, the exact order of events is poorly understood, it is generally accepted that both disorders are linked to obesity, subclinical inflammation, and insulin resistance[2].

In this current research to evaluated the safety and efficacy of *Mukia Maderaspatana* (*M. maderaspatana*) Linn leaves using a HFD emulsion produced NASH in Albino rats.

MATERIALS AND METHODS

Establishment of High Fat Diet Emulsion

A high-fat emulsion was prepared by using various edible oils, cholic acid and cholesterol with the reference to existing literatures. Multiple formulations were prepared and evaluated before the final formulation. The final emulsion contains 62% of fat content, 10% of tween 80 and sufficient amount of water. The composition of high Fat diet emulsion is presented in table 1.

Measured quantity of Corn oil, Palm oil, and Hydrogenated vegetable oil were taken in a 200 mL beaker and cholesterol was poured into the beaker (oil phase). The mixture was stirred well by magnetic stirrer (Manufactured by Remi sales & Engineering Pvt ltd) at 1500 rpm. Cholic acid was

dissolved in propylene glycol with the aid of heat and then added to the oil phase. Simultaneously, tween 80 was mixed with water phase in a beaker containing oil phase. This mixture was homogenized thoroughly to get the high fat emulsion preparation[3].

Table 1: Ingredients used in high-fat emulsion formulation

S. No	Ingredients	Proportion of Ingredients (%)
1	Corn oil	30%
2	Palm oil	10%
3	Hydrogenated vegetable oil	20%
4	Cholesterol	1.5%
5	Cholic acid	0.5%
6	Tween 80	10%
7	Propylene glycol	Q.S
8	Distilled water	Q.S
	Total energy	**656 Kcal**

Collection of plant

The leaves of *M. maderaspatana* were collect in the area of Sivakasi, Virudhunagar Dist, Tamil Nadu, India. It was authenticated by the Centre for Research and Postgraduate, Department of Botany, ANJA College, Sivakasi.

Extract Preparation

Leaves were cleaned, shadow dried and coarsely powdered. The powdered leaves were transferred into a Stoppered flask container and soaked in 70% v/v ethanol + water (1:1 ratio; 750 mL + 750 mL) for 48 hours. During this time, the flask was shaken well, hourly for first six hours, then shaken well once in 12 hours for remaining time[4]. At the end of 48 hours, the extract was filtered, and heated at 30^{0}C for 60 mins. The excessive amount of solvent was dried to evaporate using rotary evaporator. Crude extract was collected and stored at -20^{0}C for further studies.

The final residue was obtained and calculated the percentage yield[4].

Percentage yield (%w/w) = (weight of extract (g) / weight of plant material used (g)) x 100

Preliminary phytochemical analysis

The phytochemical analysis of extract of *M. maderaspatana* was performed by using the methods as described in the textbook "Phytochemical Methods A Guide to Modern Techniques of Plant Analysis" [5].

Experimental Studies

Healthy male rats (150-200gm) used for this research. The animal was maintained under controlled room temperature (25±2^{0}C) on 12hr light and 12hr dark cycle with free access to laboratory diet food and water *ad libitum*[6]. The rats were placed in polypropylene cages and allowed to acclimatize one week prior to treatments. The study was prior approved by the IAEC (Ref.No: SBCP/2022-23/CCSEA/IAEC/I(2)/F16/367).

Procedure

The rats were divided into five groups. All the group have received the emulsion of high fat diet 10 mL/kg/day (p.o.) followed by iron supplement was administrate in last week of the study and saline was given to control group for daily by oral route. The duration of study was 12 weeks. Treatment protocol was mention in the table 2.

Biochemical Parameters

End of treatment, the blood samples were collected by retro orbital plexus under suitable anesthesia. The serum was separate by using centrifuge and used to identify the biochemical analysis such as SGOT, SGPT, Cholesterol, Triglycerides, HDL-c, LDL-c, VLDL -c and Total Bilirubin[6]. Treatment protocol was mention in the table 2.

Table 2: Animal grouping and treatment protocol

Group No.	Animal Groups	Drug and Dose
I	Normal Control	Animals treated with 0.9% saline, 5 mL/kg (p.o)
II	Negative Control	Animals treated with High Fat Diet emulsion 10 mL/kg (p.o)
III	Standard	Animals treated with High Fat Emulsion10 mL/kg (p.o) for 12 weeks + Standard drug Silymarin 100 mg/kg (p.o) for last 5 weeks
IV	Test Dose 1	Animals treated with High Fat Emulsion 10 mL/kg (p.o) + Hydroalcoholic extract of *M. maderaspatana* Linn leaf 100 mg/kg (p.o)
V	Test Dose 2	Animals treated with High Fat Emulsion 10 mL/kg (p.o) + Hydroalcoholic extract of *M. maderaspatana* Linn leaf 200 mg/kg (p.o)

RESULTS

The percentage yield of hydroalcoholic extract of *M. maderaspatana* Linn (HEMM) leaf powder was 4.46% w/w. Preliminary phytochemical analysis revealed the presence of carbohydrate, proteins, tannins, saponin, flavonoids, steroids, alkaloids and phenolic compounds.

Group II animals showed a significantly increased percentage body weight compare with normal. Remaining groups like group III to V shown significantly decrease compared with group II. Results were shown in the table 3.

The animal's food intake differed followed by high-fat diet emulsion administration and drug treatments. The food intake was decreased in group II when compared to group I.

In group II (Negative control) animals showed a significant decrease in food intake When compared to group I animals. In treatment groups, Group III (standard), HEMM (100mg/kg) and HEMM (200mg/kg) animals receiving pharmacological treatments was shown significantly increase in food intake when compared to group II animals. The result showed in the table 4.

The intake of water by animals varies followed by high fat diet emulsion and drug treatments. When compared to group I animals, Water intake was decreased in group II. In treatment groups, Group III (standard), HEMM (100 mg/kg) and HEMM (200 mg/kg) animals receiving pharmacological treatments was shown significantly increase in water intake when compared to group II animals (table 5).

Table 3: Effect of HEMM leaf on Body weight and Body weight ratio of High Fat Diet Emulsion induced Steatohepatitis in Albino rats

Group	Treatment	Initial Body Weight (First Day of 1st Week)	Final Body Weight (Last day of 12th Week)	% Changes of Body Weight
I	Normal Control (0.9% Saline 5 mL/kg; p.o)	175.6±5.51	183.7±1.45	8.1%
II	Negative control (High fat emulsion 10 mL/kg; p.o)	260±2.37*	300.5±2.33*	40.5%
III	Standard (Silymarin 1 00 mg/kg; p.o)	182.3±1.22*	198.9±1.32*	16.6%
IV	Test dose 1: (*M. maderaspatana* leaf extract 100 mg/kg (p.o)	186.7±5.74*	214.4±1.28*	27.4%
V	Test dose 2: (*M. maderaspatana* leaf extract 200 mg/kg; p.o)	210.7±5.74*	225.4±1.28*	14.7%

Table 4: Effect of HEMM leaf on Food Intake of High Fat Diet Emulsion induced Steatohepatitis in Albino rats.

Group	Treatment	Food Intake (gm/day)
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	8.93±3.15
II	Negative control: High fat emulsion (10 mL/kg; p.o)	5.81±2.03**
III	Standard: Silymarin (1 00 mg/kg; p.o)	7.67±3.86**
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	6.21±2.29*
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	7.32±2.77**

Table 5: Effect of HEMM leaf on Water Intake of High Fat Diet Emulsion induced Steatohepatitis in Albino rats.

Group	Treatment	Water Intake in mL				
		Week 1	Week 3	Week 6	Week 9	Week 12
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	23.3 ± 0.30	23.43 ± 0.39	23.86 ± 0.57	24.57 ± 0.43	24.89 ± 0.31
II	Negative control: High fat emulsion (10 mL/kg; p.o)	22.98 ± 0.42	22.23 ± 0.67	21.6 ± 0.61	19.27 ± 0.30	17.73 ± 0.32
III	Standard: Silymarin (1 00 mg/kg; p.o)	23.11 ± 0.37	23.32 ± 0.50	23.63 ± 0.51	22.99 ± 0.35	24.72 ± 1.02
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	22.57 ± 0.42	22.31 ± 0.21	22.03 ± 0.46	21.32 ± 0.31	21.68 ± 0.58
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	23.87 ± 0.34	24.02 ± 0.55	4.39 ± 0.23	24.61 ± 0.65	24.71 ± 0.65

Table 6: Effect of HEMM leaf on Hemotological parameters of High Fat Diet Emulsion induced Steatohepatitis in Albino rats

Group	Treatment	WBC (x10³/µL)	RBC (x10⁶/µL)
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	14.10±0.94	7.75±0.86
II	Negative control: High fat emulsion (10 mL/kg; p.o)	26.32±0.15*	5.89±0.29*
III	Standard: Silymarin (1 00 mg/kg; p.o)	14.75±0.12***	7.98 ± 0.23***
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	16.24±1.67**	6.93±0.27**
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	4.86±0.34***	7.57±0.89***

Table 7: Effect of HEMM leaf on Biochemical parameters of SGOT and SGPT level of High Fat Diet Emulsion induced Steatohepatitis in Albino rats

Group	Treatment	SGOT (IU/L)	SGPT (IU/L)	Total Bilirubin
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	45.38±1.8	29.8±1.59	0.74±0.23
II	Negative control: High fat emulsion (10 mL/kg; p.o)	110.46±0.96*	90.97±1.12*	1.93±0.64*
III	Standard: Silymarin (1 00 mg/kg; p.o)	49.13±1.79***	33.38±0.83***	0.91±0.31***
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	73.89±0.91**	50.34±0.76**	1.35±0.32*
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	55.54±0.85***	42.45±0.72**	1.62±0.67**

Table 8: Effect of HEMM leaf on Lipid profile parameters of Triglycerides and Cholesterol of High Fat Diet Emulsion induced Steatohepatitis in Albino rats

Group	Treatment	Triglycerides (mg/dl)	Total Cholesterol (mg/dl)
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	85.89±1.32	74.42±1.89
II	Negative control: High fat emulsion (10 mL/kg; p.o)	252.8±1.63	252.13±1.97
III	Standard: Silymarin (1 00 mg/kg; p.o)	88.42±1.72***	82.85±0.56***
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	165.23±3.41*	154.86±2.31*
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	101.25±3.16**	102.23±2.13**

Table 9: Effect of HEMM leaf on Lipid profile parameters of HDL and LDL and VLDL level of High Fat Diet Emulsion induced Steatohepatitis in Albino rats

Group	Treatment	HDL (mg/dl)	LDL (mg/dl)	VLDL mg/dl
I	Normal Control: 0.9% Saline (5 mL/kg; p.o)	32.43±1.72	22.12±1.92	17.18±0.24
II	Negative control: High fat emulsion (10 mL/kg; p.o)	21.09±4.68*	95.58±4.57***	50.56±0.32**
III	Standard: Silymarin (1 00 mg/kg; p.o)	35.17±2.61**	32.74±2.34**	20.68±0.39***
IV	Test dose 1: *M. maderaspatana* leaf extract (100 mg/kg p.o)	26.12±1.67*	75.69±3.23*	33.05±0.65*
V	Test dose 2: *M. maderaspatana* leaf extract (200 mg/kg; p.o)	30.14±2.59**	51.04±2.33*	24.25±0.63**

Effect of HEMM on Hematological and Biochemical parameters

In normal control group the WBC Count was found to be 14.10 x10^3/µL. The negative control group animals WBC Count were altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals had significantly increased (26.32 x10^3/µL) WBC Count. In treatment groups, group III (standard), group IV (HEMM 100mg/kg), group V (HEMM 200mg/kg) animals were receiving pharmacological treatments showed a significantly decreased WBC Count to 16.24 x10^3/µL and 4.86 x10^3/µL respectively. See table 6.

In control group, the RBC Count was found to be 7.75 x10^6/µL. The negative control group animals RBC Count were altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals had significantly decreased (5.89 x10^6/µL) RBC Count. In treatment groups, group III (standard), group IV (HEMM 100mg/kg), group V (HEMM 200mg/kg) animals were receiving pharmacological treatments showed a significantly increased RBC Count to 6.93 x10^6/µL and 7.57 x10^6/µL respectively. Results shown in the table 6.

In normal, SGOT level was found to be 45.38 IU/L. The negative control group animals SGOT level were altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals had significantly increased (110.46 IU/L) SGOT level. In treatment groups, group III (standard), group IV&V were receiving treatments showed a significantly decreased SGOT level to 73.89 IU/L and 55.54 IU/L respectively. The data were shown in the table 7.

Normal control group of SGPT level was found to be 29.8 IU/L. The negative control group animals SGPT level were altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals had significantly increased (90.97 IU/L) SGOT level. In treatment groups, group III (standard), group V & IV were receiving pharmacological treatments showed a significantly decreasing SGPT level to 50.34 IU/L and 42.45 IU/L respectively. The results were shown in the table 7 and figure 1.

The normal control group of total bilirubin level was found to be 17.18 mg/dl. The negative control group animal's total bilirubin level was altered by High fat diet emulsion. When

compared to Group I animals, Group II (negative control) animals had significantly increased (50.56 mg/dl) total bilirubin level. In treatment groups, group III (standard), group IV (HEMM 100mg/kg), group V (HEMM 200mg/kg) animals were receiving pharmacological treatments were exhibit significantly decreased total bilirubin level to (33.05 mg/dl) and (24.25 mg/dl) respectively. The results were showed in the table 7 and figure 1.

The normal control group total cholesterol (TC) level was found to be 74.42mg/dl. The negative control group animal total cholesterol level was altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals were exhibit significantly increased (252.13 mg/dl) TC level. In treatment groups, group III (standard), group IV (HEMM 100mg/kg), Group V (HEMM 200mg/kg) animals were receiving pharmacological treatments showed a significantly decreased TC level to 154.86 mg/dl and 102.23 mg/dl respectively. The results were shown in the table 8 and figure 2.

The normal control group of triglycerides (TG) level was found to be 85.89 mg/dl. The negative control group animal triglycerides level was altered by High fat diet emulsion. When compared to Group I animals, Group II (negative control) animals had significantly increased (252.13 mg/dl) triglycerides level. In treatment groups, group III (standard), group IV (HEMM 100mg/kg), group V (HEMM 200mg/kg) animals were receiving pharmacological treatments showed a significantly decreased triglycerides level to (165.23 mg/dl) and (101.25 mg/dl) respectively. The report was showed in the table 8 and figure 2.

The Negative control of HDL-c was decreased compared with normal, whereas, LDL and VLDL-c were increased in disease induced animals compared to normal animals. The HDL-c was increased in standard and other cholesterol were decreased. See table 9 and figure 2.

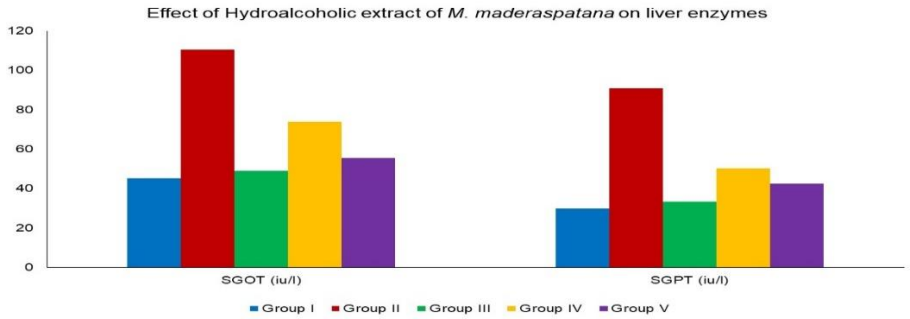

Figure 1: Effect of hydroalcoholic extract of *M. maderaspatana* on liver enzymes

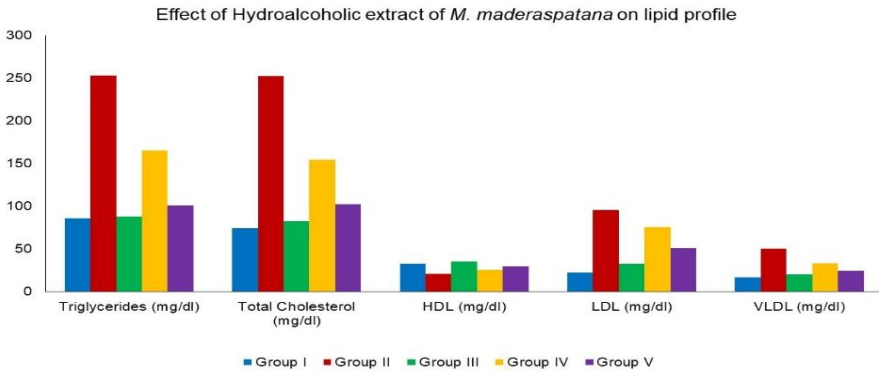

Figure 2: Effect of hydroalcoholic extract of *M. maderaspatana* on lipid profile

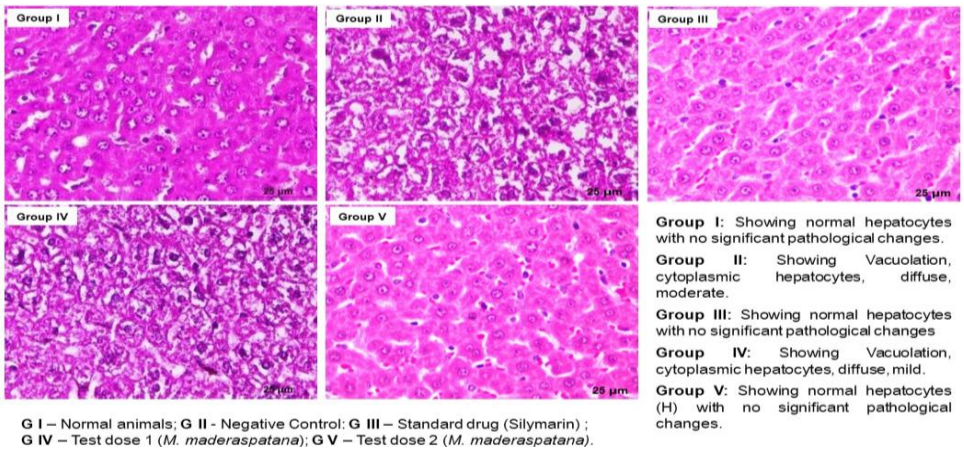

Figure 3: Histopathological report of NASH induced animals and animals group treated with standard and test drug

We observed that the weight ranges of liver were obtained from 1.96 to 4.94 gm in this study.

The liver section from the healthy control showed a normal histological pattern. The animals received High fat diet emulsion treatment exhibit vacuolation and diffused cytoplasmic hepatocytes (10mL/kg p.o). The histological pattern in the rats showed standard silymarin (100mg/kg p.o) and HEMM (200 mg/kg) is normal. The rats received (100 mg/kg) treatment demonstrates that the structure was mild vacuolation and diffuses cytoplasmic hepatocytes. The images of the liver were showed in Figure 3.

DISCUSSION

The symptoms of Non-alcoholic Steatohepatitis include fatty liver, hepatic inflammation, hepatocyte damage, and fibrogenesis. This condition may eventually progress to cirrhosis. Although there is currently no recognized pharmaceutical treatment for Non-alcoholic Steatohepatitis, current management of the condition involves weight loss and increased physical exercise[7].

In the present study, High Fat diet emulsion induced Non-alcoholic Steatohepatitis animal model have potent activity due to animal become obese so gradually enhance abnormal body weight and abnormal secretion of enzymes levels and shows the abnormal lipid profile parameters. The liver weight was observed by *in vivo* studies.

Under normal dietary conditions, palm oil affects the homeostasis synthesis. The High fat diet and inter esterified palm oil boost the glucose synthesis and fatty acid accumulation in the liver[8]. Serum ALP levels increased only when palm oil was cooked once and five times. According to histology, a diet high in palm oil produces liver inflammation and micro steatosis but not necrosis.

Heating had no effect on the liver histological alterations. Inflammation, micro steatosis, and increased liver enzyme like ALT and ALP in all cause by a high-fat diet[9]. Bile acids (BAs) such as cholic acid affect the lipid and glucose metabolism, inflammation, and fibrosis[10].

Oral administration of High fat diet 10mL/kg attributed to the steatosis and inflammation and cirrhosis and oxidative damage caused by the high level of abnormal lipid metabolism and mitochondrial dysfunction, endoplasmic reticulum stress and lipo toxicity generated. Body weight was enhanced in High fat emulsion (Negative control) induced group was observed and have a change in BW of HEMM. Liver function study, also observe the increased liver enzymes level in particularly High fat emulsion induced animals, indicating that obstruction of liver hepatocytes due to intake high fat content.

A decreased in the abnormal count liver enzymes level was observed on drug treated groups indicating its antifibrotic activity.

After administration of High fat diet emulsion decreased the red cell count and increased the white cells compare to normal group, after administration of Silymarin and *M. maderaspatana* leaf extract significantly changes there in RBC and WBC.

Administration of high fat diet emulsion the altered lipid profile values. After the therapy of Silymarin and *M. maderaspatana* leaf extract significantly decreased the cholesterol parameter except HDL.

The liver enzyme levels were increased when after administration of high fat diet. Treatment with Silymarin and *M. maderaspatana* leaf extract significantly decreased the biochemical parameters when compare to Negative Control.

Histopathological evaluation showed, animals treated with Silymarin and *M. maderaspatana* leaf extract at 200 mg/kg exhibited maximum prevention of fat deposition.

CONCLUSION

The present study results confirmed the alkaloids, flavonoids, tannins, glycosides, saponin, carbohydrates and proteins in *M. maderaspatana* leaf. The leaf of HEMM(200 mg/kg) (p.o.) had shown the significant effect on reducing lipid profiles and improving the biochemical parameters in animals induce with non-alcoholic steatohepatitis. The plant may have the potency to slow down the progression of non-alcoholic steatohepatitis, prevention of hepatic cell death, and lessen the metabolic and pathological abnormalities developed in the non-alcoholic steatohepatitis animal model. The study further warrants for isolation, and characterization of these phytoconstituents which can be developed further for clinical use.

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OBBERVATION

HEMM - Hydroalcoholic extract of *M. maderaspatana* Linn

MM - *M. maderaspatana*

HDL-c - High density lipoprotein cholesterol

LDL-c - low density lipoprotein cholesterol

VLDL-c - Very low-density lipoprotein cholestrol

NASH - nonalcoholic steatohepatitis

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