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Antioxidant and Antihyperlipidemic Activities of Methanolic Extract of *Rubia cordifolia* Roots

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ABSTRACT

Hyperlipidemia, characterized by elevated cholesterol and triglyceride levels, poses a significant global health challenge with substantial implications for cardiovascular well-being. This study investigated the anti-hyperlipidemic potential of the methanolic root extract of *Rubia cordifolia* (MERC) using rat models induced with hyperlipidemia through a high-fat diet. Hyperlipidemia was induced by administering a high-fat diet to rats for a duration of 4 weeks. MERC exhibited notable antioxidant activity in DPPH and reducing power assays. Treatment with MERC at doses of 200 and 400 mg/kg orally significantly mitigated hyperlipidemia, evidenced by reduced levels of serum Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDLC), and an increase in serum High-Density Lipoprotein Cholesterol (HDLC) compared to the vehicle control and the standard drug Atorvastatin. These findings underscore the substantial anti-hyperlipidemic activity of the methanolic root extract of *Rubia cordifolia*.

Keywords: *Rubia cordifolia*, hyperlipidemia, antioxidant, toxicity, cholesterol.

1. INTRODUCTION

Hyperlipidemia, marked by elevated levels of cholesterol and triglycerides, stands as a formidable global health challenge with profound implications for cardiovascular health. Its complex pathophysiology, influenced by genetic predispositions and lifestyle factors, leads to atherosclerosis, increasing the risk of debilitating complications like coronary artery disease and strokes. The widespread prevalence of hyperlipidemia, closely tied to dietary habits and aging, underscores the urgent need for comprehensive understanding and management.[1,2]

Accurate diagnosis through lipid profile assessments guides interventions aimed at mitigating complications. While lifestyle modifications, including dietary changes and increased physical activity, form the cornerstone of management, pharmacotherapy, such as statins, plays a crucial role in achieving optimal lipid levels. However, drawbacks persist, ranging from medication side effects to challenges in long-term adherence and financial constraints. Addressing hyperlipidemia's impact requires a holistic approach, integrating preventive measures, tailored interventions, and ongoing research to optimize global cardiovascular health.[3]

In the context of hyperlipidemia, the role of antioxidants becomes particularly relevant. Elevated levels of lipids, such as cholesterol and triglycerides, can contribute to oxidative stress, leading to an increased production of free radicals. This oxidative imbalance is a crucial factor in the progression of atherosclerosis, a condition closely associated with hyperlipidemia.[4] Antioxidants play a significant role in mitigating this risk by neutralizing free radicals and preventing cellular damage. A diet rich in antioxidants, obtained from sources like fruits, vegetables, and whole grains, can offer protective effects against the oxidative stress induced by high lipid levels. Incorporating antioxidants into the

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management strategy for hyperlipidemia may provide additional support in reducing the risk of cardiovascular complications associated with this condition, emphasizing the interconnectedness of diet, oxidative balance, and lipid metabolism in maintaining cardiovascular health.[5]

Rubia cordifolia (RC), commonly known as Manjistha or Indian madder, is a plant belonging to the Rubiaceae coffee family and is indigenous to the lower Himalayas, India, Japan, Indonesia, and Sri Lanka.[6] Traditionally used as a red pigment, this herb has found extensive application in Ayurvedic medicine for treating conditions such as jaundice, joint inflammation, and cough. It is rich in anthraquinones, naphthoquinones, anthraquinone & naphthoquinone glycosides, bicyclic hexapeptides, triterpenoids and polysaccharides.[7] Notably, *Rubia cordifolia* has gained popularity in Western cultures as an alternative therapy for skin conditions like eczema, psoriasis, and dermatitis. The plant has been recognized for its significant antioxidant effects both *in vitro* and *in vivo*, making it a subject of interest for potential therapeutic applications. Preliminary studies have also suggested its potential as an inhibitory agent against breast cancer cell proliferation. It is used as anti-inflammatory, neuroprotective, radioprotective, anti-diabetic, hepatoprotective, antibacterial, anti-HIV, anti-adipogenic, and anti-ulcer activities.[8-11]

The presence of anthraquinone compounds in the root of *Rubia cordifolia* has sparked interest in assessing the plant's potential antioxidant activity. Given that lipids are highly susceptible targets for free radicals, their oxidative destruction, known as lipid peroxidation, the present study evaluates the antihyperlipidemic activity of the methanolic extract derived from the roots of *Rubia cordifolia* (MERC) in high cholesterol induced diet in Wistar rats. This dual focus reflects a comprehensive exploration of the plant's bioactive & antioxidant properties, shedding light on its potential benefits in mitigating oxidative stress and addressing lipid-related disorders.

2. MATERIAL & METHODS

2.1 Chemicals and Drugs

The chemicals and kits utilized in the study were sourced from various reputable companies, contributing to the reliability of the experimental data. Premier Pvt Ltd in India provided the crucial component, cholesterol. Atorvastatin (40 mg) was supplied by Cipla Ltd., India, while sucrose and methionine were obtained from SD Fine Chem Ltd, India. The biochemical diagnosis testing kits were sourced from Tulip Diagnostics (P) Ltd., while all remaining chemicals were procured from established and reputable suppliers.

2.2 Collection and Extraction of Plant Material

The roots of *Rubia cordifolia* was collected from Shimoga forest area situated in Karnataka, India. Fresh and healthy root parts were collected and thoroughly washed, and shade dried for 15–20 days at room temperature (25°C ± 2°C), further pulverized to powdered form. The root powder was extracted using methanol for 18 h using Soxhlet apparatus. The resulting extract was then stored in an airtight container at room temperature for future use. The condensed extract was used for preliminary screening to determine the presence of bioactive compounds using the standard qualitative procedures.

2.3 Evaluation of Antioxidant Activity

The ability of the extracts to scavenge DPPH (1,2-diphenyl-2-picrylhydrazyl) radical and its reducing power was determined at different concentrations as per the established procedures.[12] Ascorbic acid was used as standards for the various *in vitro* antioxidant studies.

2.4 Acute Toxicity Studies

Methanolic extract of roots of *Rubia cordifolia* (MERC) was used for acute toxicity study on female albino Wistar rats according to OECD guidelines 423. Animals were fasted prior to dosing, food but not water was withheld overnight. Following the period of fasting, the animals were weighed, and the test substance was administered. After the substance had been administered, food was withheld for a period of 3-4 hrs. Three animals were used for each step. The dose level of MERC to be used as the starting dose was selected from one of the four fixed levels (5, 50, 300 and 2000 mg/kg b.w., p.o). The starting dose level was that which was most likely to produce mortality in some of the dosed animals. After administration of test sample, the animals were observed continuously for the first 4hrs, for the

behavioral changes and at the end of 24 hrs, for mortality, if any.[13]

2.5 Experimental Animals

The experimentation involving animals received approval from the Institutional Animal Ethics Committee (IAEC) at Shadan College of Pharmacy, Ranga Reddy District, Telangana, India. The establishment of the IAEC adhered to the guidelines set forth by the Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Animal Welfare Division, Government of India. For the study, male albino Wistar rats weighing between 120 and 150 g were specifically chosen. The Wistar rats were housed in standard laboratory conditions at a temperature of 25°C ± 2°C and were provided with a standard pellet diet, with access to water throughout the duration of the experiment.

2.6 Evaluation of Anti-hyperlipidemic Activity

Female albino rats were divided into five groups with 6 rats in each group that will be matched for body weight, after 1 week of being fed with laboratory normal pellet diet (Table 1). Hyperlipidemia was induced by increasing blood cholesterol levels using the earlier modified method of Onody *et al.,* 2003.[14] Briefly, cholesterol (2% w/w) powder was thoroughly mixed with crushed pellet diet and reconstituted with water and allowed to dry properly to prevent microbial contamination.

Table 1: Grouping of experimental animals

S. No.	Groups	Treatment
1	Group I (Control)	Normal pellet diet
2	Group II (Hyperlipidemic)	High fat diet (Cholesterol powder 2% w/w)
3	Group III (Standard)	High fat diet + Atorvastatin (30 mg/kg b.w./day)
4	Group IV (Treatment I)	High fat diet + MERC (200 mg/kg/day)
5	Group V (Treatment II)	High fat diet + MERC (400 mg/kg/day)

The solution of extract was prepared freshly every day and given to their respective group at 3.00 pm. This process was followed for 4 weeks, and the amount of food intake was monitored daily. At the end of experimental studies, animals were fasted for 12 hr and the blood was collected by venous puncture and then sacrificed by ether anesthesia. The biochemical parameters such as total cholesterol (TC), low density lipoproteins (LDL), triglyceride levels (TG) and high-density lipoproteins (HDL) were evaluated using standard diagnostic kits.

2.7 Experimental Procedure

The enzymatic method outlined by Allain et al. in 1974 was employed for the estimation of total cholesterol in the plasma, erythrocytes, and tissues.[15] The diagnostic kit, based on the enzymatic method detailed by McGowan et al. in 1983, was utilized for the estimation of triacylglycerol in both the plasma and tissues.[16] The estimation of HDL-cholesterol was carried out using a diagnostic kit founded on the enzymatic method as described by Izzo et al. in 1981.[18] LDL cholesterol was estimated by the standard formula as follows and was expressed as mg/dl.

$$LDL = TC - (HDL + VLDL)$$

LDL = Low Density Lipoproteins

TC = Total Cholesterol

HDL = High Density Lipoproteins

VLDL = Very Low-Density Lipoproteins

2.8 Statistical Analysis

The results for all parameters were presented as the mean ± standard error of the mean (SEM) and subjected to analysis through one-way ANOVA, followed by Dunnet's multiple comparison test. Significance between groups was determined at the $P < .05$ levels.

3. RESULTS

3.1 Preliminary Phytochemical Screening

The preliminary phytochemical analysis of methanolic extracts of roots of *Rubia cordifolia* indicated the presences of alkaloids, quinones, phenol, glycosides, carbohydrates, and free anthraquinones.

3.2 Acute Toxicity Studies

The methanolic extract of roots of *Rubia cordifolia* was found to be safe at the maximum tested dose of 2000 mg/kg body weight by oral route. After 24 hours, animals were found well tolerated and there was no mortality. All the concentrations of extracts were found to be safe, Thus, 1/10th and 1/5th dose of 2000 mg/kg b.w. i.e., 200 mg and 400 mg/kg b.w.

was taken as effective dose for treating hyperlipidemia in experimental animal.

3.3 Evaluation of Antioxidant Activity

The extract produced significant DPPH radical scavenging activity from 10 µg/ml. The IC_{50} (mean ± µg/ml, the reducing power of ascorbic acid and MERC showed maximum antioxidant activity. Reducing power of MERC at 500 µg/ml was comparable ($P < .05$) to that of ascorbic acid (Fig. 1).

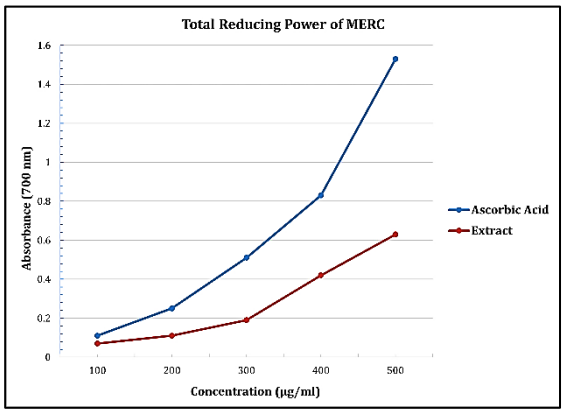

Fig. 1: Total reducing power of different concentrations of MERC

3.4 Effect of MERC on Weight Gain

Table 2 shows that there were significant differences ($P < 0.01$) in the weight gain pattern of the animals fed with high cholesterol diet as compared to normal control. Co-treatment with methanolic extract of leaves of *Rubia cordifolia* (200 and 400 mg/kg b.w.) and standard drug to rats on high cholesterol diet significantly ($P < 0.0001$) restored the weight gain pattern to near normal. The extract activity is dose dependent, and it compared favorably with the standard drug.

3.5 Effect of MERC on Serum Lipid Profile

The results of the present investigation show that rats fed with cholesterol rich diet developed hypercholesterolemia with a significant ($P < 0.0001$) increase in TC, LDL, TG, and a significant ($P < 0.0001$) decrease in HDLC levels as compared to the control rats (Fig. 2). However, co-administration MERC (200 and 400 mg/kg b.w.) and standard drug atorvastatin to high cholesterol fed rats significantly ($P < 0.0001$) decreased the level TC, TG, LDL and cause a significant increase in the level of HDLC when compared with the hyperlipidemic group (Fig. 2).

4. DISCUSSION

Traditional medicine, a constantly evolving process, witnesses the ongoing discovery of innovative techniques that can revolutionize life practices.[19] According to the World Health Organization (WHO), herbal medicine caters to the health needs of approximately 80% of the global population. Concurrently, individuals in developing nations are growing disillusioned with modern healthcare and turning to alternatives. The recent resurgence of plant-based remedies can be attributed to factors such as the efficacy of plant medicines, the side effects associated with synthetic drugs, and advancements in science and technology.[20,21]

Obesity and hyperlipidemia result from elevated cholesterol levels in the body, contributing to increased total cholesterol and the potential risk of diabetes and cardiovascular diseases. Herbs play a pivotal role in managing obesity, with various medicinal plants and formulations employed in ethnomedical practices and traditional medicine in India. Despite the prevalence of herbal remedies, satisfactory solutions for hyperlipidemia remain elusive, with most herbal drugs reducing cholesterol through healthy dietary intake.[22] Therefore, the present study aimed to investigate the anti-hyperlipidemic activity of methanolic root extract of

Table 2: The effect of methanolic root extract of *Rubia cordifolia* on weight gain of experimental animals

Group	No. of Days		
	Day 0	Day 14	Day 28
Control	257 ± 0.88	256 ± 0.92	256 ± 0.76
Hyperlipidemic	255 ± 0.81	259 ± 1.4***	264 ± 0.89***
Standard	258 ± 0.64	260 ± 0.51***	261 ± 0.76***
Treatment I	255 ± 1.02	258 ± 0.83***	260 ± 0.87***
Treatment II	257 ± 0.62	258 ± 0.53**	259 ± 0.41***

*The values are expressed as mean ± SEM (n=6). ***P < 0.001, **P < 0.01, *P < 0.05 compared to the Day 0. Data were analyzed by one-way ANOVA, followed by Dunnett's Multiple Comparison test.*

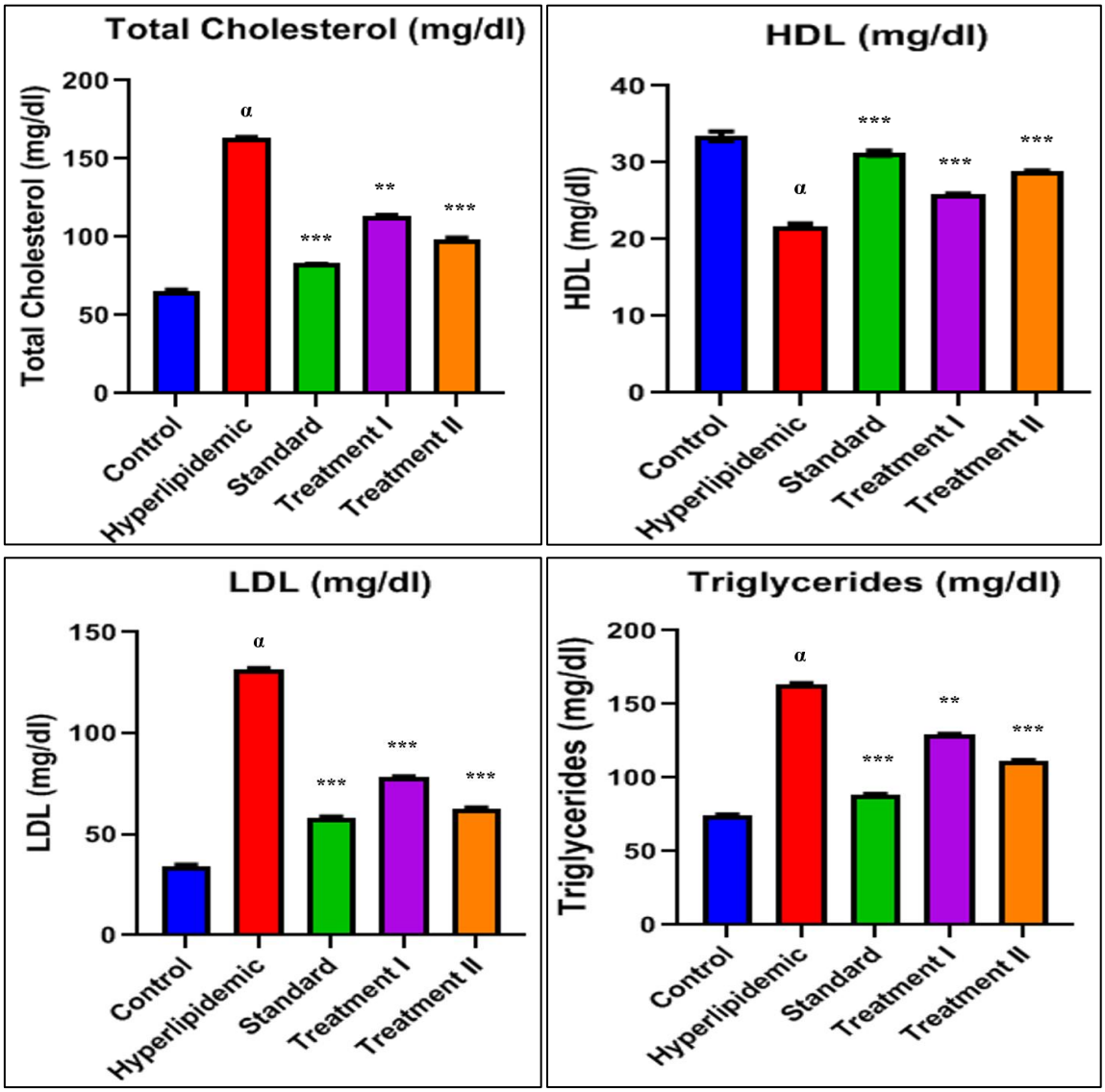

Fig. 2: Effect of MERC on the serum lipid profile

*The values are expressed as mean ± SEM (n=6). ᵅP < 0.001 when compared to control group and ***P < 0.001, **P < 0.01, *P < 0.05 compared to the hyperlipidemic group. Data were analyzed by one-way ANOVA, followed by Dunnett's Multiple Comparison test.*

Rubia cordifolia (MERC) in rats induced with high cholesterol diet.

The Soxhlet method was employed to extract roots of *Rubia cordifolia*. Preliminary phytochemical screening revealed the presence of alkaloids, quinones, phenol, glycosides, carbohydrates, and free anthraquinones. The study evaluated the extract's efficacy in scavenging DPPH radical and its reducing power across different concentrations.

The antioxidant potential of the MERC was found to be significant with standard ascorbic acid. The extract, deemed safe up to a dose of 2000 mg/kg body weight, was administered orally at dose levels of 200 mg/kg and 400 mg/kg. A four-week feeding study with rats aimed to elucidate the impact of a high-fat diet on serum lipid profiles, given the differences observed between rodents and humans in response to cholesterol and dietary changes.[22] The study induced hyperlipidemia in rats through a 2% cholesterol diet, leading to increased total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels, along with decreased high-density lipoprotein (HDL) levels. The induction of hyperlipidemia in rats through a 2% cholesterol diet involves a multifaceted pathophysiological process. The increased dietary cholesterol intake leads to elevated levels of low-density lipoprotein (LDL) cholesterol, commonly known as "bad cholesterol," promoting the accumulation of cholesterol in arterial walls and the formation of atherosclerotic plaques.

Simultaneously, triglyceride levels rise, contributing to the overall dysregulation of lipid metabolism. This dietary challenge also results in a reduction in high-density lipoprotein (HDL) cholesterol, the "good cholesterol," impairing its ability to effectively remove excess cholesterol from the bloodstream. The imbalance in lipid profiles induces oxidative stress and inflammation, exacerbating the progression of cardiovascular complications. This experimental model provides a valuable platform for investigating the intricate mechanisms underlying hyperlipidemia and its associated cardiovascular risks, offering insights into potential therapeutic interventions.[23-25]

The present study revealed significant alterations in the weight gain pattern of rats fed with a high-cholesterol diet, indicative of the impact of dietary cholesterol on metabolic parameters. Co-treatment with methanolic extract of leaves of Rubia cordifolia (MERC) at doses of 200 and 400 mg/kg b.w., along with the standard drug, demonstrated a remarkable restoration of the weight gain pattern to near normal levels. This dose-dependent effect of the extract, comparable to the standard drug, suggests its potential in mitigating the adverse effects of high cholesterol.

The biochemical analysis further supported these findings, showing that the rats on a cholesterol-rich diet developed hypercholesterolemia, characterized by a significant increase in TC, LDL, and TG, coupled with a significant decrease in HDLC. Co-administration of MERC and atorvastatin significantly reversed these lipid profile alterations, emphasizing the potential of MERC in attenuating hyperlipidemia. The observed effects may be attributed to the extract's ability to modulate lipid metabolism, possibly through mechanisms involving cholesterol synthesis, transport, or metabolism regulation.

Anthraquinones, natural compounds found in various plants, exhibit potential in reducing hyperlipidemia through inhibition of cholesterol synthesis in the liver, potentially modulating key enzymes involved in biosynthesis. Anthraquinones may also enhance the excretion of cholesterol through bile acids, facilitating the elimination of excess cholesterol from the body. Their antioxidant properties contribute to counteracting oxidative stress and inflammation associated with hyperlipidemia. Furthermore, anthraquinones may regulate lipid metabolism by influencing the activity of enzymes in triglyceride synthesis and breakdown. Additionally, these compounds could modulate lipoprotein metabolism, impacting the balance between low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. While these mechanisms present promising avenues, further research is necessary to comprehensively understand the specific pathways involved and to determine the efficacy and safety of anthraquinones as potential therapeutic agents for hyperlipidemia. Individual responses and clinical applications warrant careful consideration in future studies.[26,27]

5. CONCLUSION

The results obtained from the pharmacological screening have led to the conclusions that, methanolic root extract of *Rubia cordifolia* has significant antihyperlipidemic activity. Hence it can be exploited as an anti-hyperlipidemic therapeutic agent or adjuvant in existing therapy for the treatment of hyperlipidemia.

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Conflict of Interest: The authors declare that they have no conflicts of interest.

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