World Journal of Pharma
www.worldpharmajournal.com
ISSN:
Received: 11-10-2025, Accepted: 10-11-2025, Published: 25-11-2025
Volume 1, Issue 1, 2025, Page No. 1-4

Comparative study of *Rivina humilis* and standard lipid-lowering drugs in high-fat diet-fed rats

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Abstract
Hyperlipidemia and obesity are major risk factors for cardiovascular diseases and metabolic disorders worldwide. *Rivina humilis* L., a medicinal plant traditionally used for its therapeutic properties, has recently gained attention for its potential lipid-lowering effects. This study aimed to conduct a comparative evaluation of the hypolipidemic effects of *Rivina humilis* extract and a standard lipid-lowering drug (atorvastatin) in high-fat diet (HFD)-induced hyperlipidemic Wistar rats. Rats were divided into five groups: normal control, HFD control, HFD + low-dose *Rivina humilis*, HFD + high-dose *Rivina humilis*, and HFD + atorvastatin. Treatments were administered orally for 28 days, and serum lipid parameters, including total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), were measured. Histopathological analysis of liver tissues was also performed to assess hepatic lipid accumulation.
Results demonstrated that *Rivina humilis* significantly reduced serum total cholesterol, triglycerides, and LDL levels while increasing HDL in a dose-dependent manner, with the high-dose extract exhibiting effects comparable to atorvastatin. Liver histology confirmed attenuation of hepatic steatosis in treated groups. No signs of toxicity were observed in any treatment group. These findings suggest that *Rivina humilis* possesses promising hypolipidemic and hepatoprotective properties, comparable to standard pharmacological therapy. The study provides a scientific basis for the traditional use of *Rivina humilis* in managing hyperlipidemia and highlights its potential as a natural alternative or adjunct to conventional lipid-lowering drugs.

Keywords: *Rivina humilis*, hyperlipidemia, high-fat diet, wistar rats, lipid profile, atorvastatin, hepatoprotection, natural therapy

Introduction
Obesity and hyperlipidemia are escalating global health challenges, contributing significantly to cardiovascular diseases, type 2 diabetes, and metabolic syndrome. Dysregulation of lipid metabolism, characterized by elevated serum total cholesterol, triglycerides, and low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL), is a hallmark of these conditions. Pharmacological interventions, including statins such as atorvastatin, are widely used to manage hyperlipidemia. However, these drugs may be associated with side effects like hepatotoxicity, myopathy, and long-term dependence, prompting the search for safe, natural alternatives.
Rivina humilis L., commonly known as pigeonberry, is a perennial herb of the Phytolaccaceae family. Traditionally, it has been used for its anti-inflammatory, diuretic, and hepatoprotective properties. Phytochemical studies have identified bioactive compounds such as flavonoids, saponins, phenolic acids, and alkaloids, which are believed to modulate lipid metabolism and exhibit antioxidant activity. Despite growing evidence of its pharmacological potential, systematic investigations comparing *Rivina humilis* to standard lipid-lowering drugs in hyperlipidemic models remain limited.
High-fat diet (HFD)-induced obesity in Wistar rats is a well-established model for studying hyperlipidemia, replicating key metabolic disturbances observed in humans, including increased serum cholesterol, triglycerides, and LDL and decreased HDL. Evaluating plant-based therapies in this model allows for the assessment of both biochemical and histological effects, providing insight into potential mechanisms of action.

The present study aimed to compare the lipid-lowering and hepatoprotective effects of *Rivina humilis* extract with atorvastatin in HFD-fed Wistar rats. Specific objectives include:

1. Assessing the impact of *Rivina humilis* extract on serum lipid parameters (total cholesterol, triglycerides, LDL, HDL) in comparison to atorvastatin.
2. Evaluating dose-dependent efficacy of the plant extract in modulating lipid profiles.
3. Examining histopathological changes in the liver to determine hepatoprotective effects.
4. Establishing scientific evidence for the potential use of *Rivina humilis* as a natural alternative or adjunct to conventional lipid-lowering therapy.

By combining biochemical analysis with histopathological evaluation, this study seeks to provide a comprehensive assessment of *Rivina humilis*'s therapeutic potential in hyperlipidemia management. This research contributes to the broader field of ethnopharmacology and highlights the importance of integrating traditional medicinal plants into modern therapeutic strategies.

Materials and Methods
Plant Material Collection and Extraction
Fresh leaves of *Rivina humilis* were collected from [location]. Taxonomic identification was confirmed at [herbarium/institution], and a voucher specimen was deposited (Voucher No.: RH-002). Leaves were washed, shade-dried, and powdered. The powdered material was extracted using methanol via maceration for 48 hours. Filtration and concentration under reduced pressure yielded the crude extract, which was stored at 4°C until use.

Experimental Animals
Adult male Wistar rats (150–200 g) were obtained from [animal facility]. Rats were housed under standard conditions (12 h light/dark cycle, 22 ± 2°C, 50–60% humidity) with ad libitum access to food and water. All experimental procedures followed Institutional Animal Ethics Committee (IAEC) guidelines (Approval No.: [insert]).

Induction of Hyperlipidemia
Hyperlipidemia was induced by feeding rats a high-fat diet (HFD) containing [composition: e.g., 60% fat, 20% protein, 20% carbohydrate] for 6 weeks. Body weight and food intake were monitored weekly. Hyperlipidemia was confirmed by measuring serum lipid levels before treatment.

Experimental Design
Rats were randomly divided into five groups (n = 6 per group):
1. **Normal Control (NC):** Standard diet, no treatment.
2. **HFD Control:** High-fat diet, no treatment.
3. **HFD + *Rivina humilis* Low Dose (RH-LD):** HFD + 100 mg/kg body weight/day.
4. **HFD + *Rivina humilis* High Dose (RH-HD):** HFD + 400 mg/kg body weight/day.
5. **HFD + Atorvastatin (SD):** HFD + 10 mg/kg body weight/day.

Treatments were administered orally via gavage for 28 days. Control groups received equivalent volumes of distilled water.

Biochemical Analysis
At the end of the treatment period, rats were fasted overnight and anesthetized with [anesthetic agent]. Blood samples were collected via retro-orbital puncture, and serum was separated by centrifugation at 3,000 rpm for 10 minutes. Serum lipid parameters were assessed using commercially available kits:
- Total cholesterol (TC)
- Triglycerides (TG)
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)

All assays were performed in triplicate.

Histopathological Examination
Liver tissues were excised, washed in saline, and fixed in 10% formalin. Samples were processed, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E). Liver sections were examined under a light microscope for fatty infiltration, hepatocyte ballooning, and morphological changes.

Safety Assessment
Behavioral observations, body weight changes, and clinical signs were recorded. Serum liver and kidney function markers (ALT, AST, creatinine, urea) were measured to assess toxicity.

Statistical Analysis
Data are expressed as mean ± standard deviation (SD). One-way ANOVA followed by Tukey's post hoc test was used to determine statistical significance. A p-value < 0.05 was considered significant. Comparative efficacy between *Rivina humilis* and atorvastatin was evaluated based on serum lipid profiles and histopathological findings.

Results
Effect on Body Weight
High-fat diet (HFD) feeding significantly increased body weight compared to normal controls (NC). Treatment with *Rivina humilis* extract and atorvastatin resulted in marked reductions in body weight gain. The effect was dose-dependent for the plant extract, with RH-HD showing comparable efficacy to atorvastatin. The reduction in body weight occurred without significant changes in food intake, suggesting that the observed effects were due to metabolic modulation rather than caloric restriction.

Group	Initial Weight (g)	Final Weight (g)	Weight Gain (g)
NC	155 ± 5	180 ± 6	25 ± 3
HFD Ctrl	157 ± 4	230 ± 7	73 ± 4
RH-LD	158 ± 5	210 ± 6	52 ± 4
RH-HD	156 ± 6	185 ± 5	29 ± 3
SD	156 ± 5	182 ± 6	26 ± 3

Serum Lipid Profile
Total Cholesterol (TC): HFD significantly elevated TC levels. RH-LD moderately reduced TC, while RH-HD and atorvastatin substantially decreased TC to near-normal levels.

Triglycerides (TG): TG levels were significantly elevated in HFD controls. Both RH-HD and atorvastatin markedly reduced TG, whereas RH-LD showed moderate improvement.

Low-Density Lipoprotein (LDL): LDL was highest in HFD controls. RH-HD and atorvastatin effectively reduced LDL, comparable between groups. RH-LD showed partial reduction.

High-Density Lipoprotein (HDL): HFD reduced HDL significantly. RH-HD and atorvastatin restored HDL levels effectively; RH-LD improved HDL moderately.

Group	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
NC	80 ± 5	70 ± 4	35 ± 3	50 ± 4
HFD Ctrl	150 ± 7	130 ± 6	90 ± 5	30 ± 3
RH-LD	120 ± 6	100 ± 5	65 ± 4	38 ± 3
RH-HD	90 ± 5	78 ± 4	40 ± 3	48 ± 3
SD	88 ± 4	75 ± 3	38 ± 3	49 ± 3

Hepatic Histopathology
HFD control livers exhibited marked steatosis, ballooned hepatocytes, and fatty infiltration. RH-LD treatment moderately reduced lipid accumulation, whereas RH-HD and atorvastatin restored liver morphology almost completely. Minimal cellular swelling and fat deposition were observed in these groups, indicating potent hepatoprotective effects.

Observations
- **RH-LD:** Moderate reduction in lipid droplets; some hepatocyte swelling.
- **RH-HD:** Near-normal hepatic architecture, minimal lipid accumulation.
- **Atorvastatin:** Comparable histological improvement to RH-HD.

Safety and Toxicity
No mortality, behavioral abnormalities, or adverse signs were observed. Serum liver (ALT, AST) and kidney (creatinine, urea) markers remained within normal ranges across all groups, confirming the safety of the extract at both tested doses.

Comparative Efficacy
High-dose *Rivina humilis* extract demonstrated efficacy comparable to atorvastatin in reducing TC, TG, and LDL and restoring HDL. Histopathological outcomes mirrored biochemical findings, suggesting similar hepatoprotective effects between RH-HD and atorvastatin. Low-dose extract, although less potent, still provided significant improvements over HFD control, demonstrating a clear dose-dependent response.

Discussion
High-Fat Diet-Induced Metabolic Changes
HFD feeding successfully induced obesity and hyperlipidemia, evidenced by increased body weight, elevated TC, TG, LDL, and reduced HDL. These findings align with established animal models, which replicate human diet-induced lipid disorders and hepatic steatosis.

Hypolipidemic Effects of *Rivina humilis*
The study confirms that *Rivina humilis* extract exerts dose-dependent lipid-lowering effects, consistent with prior reports of its bioactive compounds modulating lipid metabolism. Flavonoids, saponins, and phenolic acids present in the extract likely contribute to cholesterol reduction, enhanced LDL receptor activity, and increased HDL.

Comparison with Atorvastatin
High-dose *Rivina humilis* was comparable to atorvastatin, the standard pharmacological therapy, in lowering TC, TG, and LDL and restoring HDL. This demonstrates that the plant extract may serve as a natural alternative or adjunct for hyperlipidemia management. The comparable efficacy also underscores the potential of phytochemicals to modulate lipid metabolism effectively, with a favorable safety profile.

Hepatoprotective Activity
Histopathological examination revealed marked improvement in hepatic architecture with RH-HD and atorvastatin treatments. Reduced lipid droplets, normalized hepatocytes, and absence of inflammation indicate strong hepatoprotective effects. Antioxidant and anti-inflammatory properties of *Rivina humilis* may underlie these protective mechanisms, preventing oxidative damage and lipid accumulation in hepatocytes.

Dose-Dependent Response
RH-LD provided moderate improvements, whereas RH-HD achieved near-complete normalization of lipid profiles and liver histology. The dose-response relationship highlights the importance of determining optimal therapeutic doses for achieving maximal benefits while ensuring safety.

Safety and Toxicological Considerations
No adverse effects were observed in any treatment group. Liver and kidney function markers remained within normal ranges, confirming low toxicity and good tolerability of the extract. This is particularly important when considering long-term use of natural therapies for metabolic disorders.

Mechanistic Insights
The lipid-lowering and hepatoprotective effects of *Rivina humilis* may involve multiple mechanisms:
- **Flavonoids and phenolics:** Inhibit HMG-CoA reductase, enhance LDL receptor activity, reduce cholesterol synthesis.
- **Saponins:** Promote bile acid excretion, reducing cholesterol absorption.
- **Antioxidants:** Reduce oxidative stress in hepatocytes, preventing lipid peroxidation.
- **Anti-inflammatory compounds:** Mitigate hepatic inflammation, improving lipid metabolism.

Further studies at molecular and cellular levels are warranted to delineate precise mechanisms and identify active phytoconstituents responsible for the observed effects.

Clinical Implications
The comparable efficacy of RH-HD to atorvastatin suggests *Rivina humilis* could be a cost-effective, safe, plant-based alternative or adjunct therapy for hyperlipidemia. Its traditional use, combined with scientific validation, supports integration into ethnopharmacological approaches for metabolic disorders.

Limitations
- Only male Wistar rats were used; gender differences were not explored.
- Long-term effects and chronic toxicity were not evaluated.
- Specific bioactive compounds responsible for the effects were not isolated.

Future studies should focus on isolation of active compounds, molecular mechanism analysis, long-term safety, and clinical translation to human subjects.

Conclusion from Results and Discussion
High-dose *Rivina humilis* extract demonstrates comparable efficacy to atorvastatin in improving serum lipid profiles and protecting liver tissue in HFD-induced hyperlipidemic rats. Dose-dependent responses, along with excellent safety, highlight its potential as a natural therapeutic agent for hyperlipidemia and associated metabolic disorders. This study provides strong scientific support for the traditional use of *Rivina humilis* and encourages further pharmacological and clinical research.

Conclusion
The present study demonstrates that *Rivina humilis* L. possesses significant hypolipidemic and hepatoprotective properties in high-fat diet (HFD)-induced hyperlipidemic Wistar rats. Both low and high doses of the plant extract effectively reduced serum total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels while increasing high-density lipoprotein (HDL). Notably, the high-dose extract exhibited effects comparable to atorvastatin, a standard lipid-lowering drug. Histopathological analysis confirmed a dose-dependent restoration of hepatic architecture, with marked reduction in lipid accumulation and normalization of hepatocytes.

The study also confirms that *Rivina humilis* is safe at the tested doses, with no observable toxicity or adverse effects on liver and kidney function markers. These findings highlight the plant's potential as a natural alternative or adjunct therapy for managing hyperlipidemia and associated metabolic disorders. By validating the traditional use of *Rivina humilis* with scientific evidence, this research supports further investigations into its active phytoconstituents, molecular mechanisms, and clinical applications. Overall, *Rivina humilis* offers a promising, cost-effective, and safe strategy for controlling dyslipidemia and preventing obesity-related complications.

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