Indonesian Journal of Global Health Research
Volume 8 Number 3, June 2026
e-ISSN 2715-1972; p-ISSN 2714-9749
http://jurnal.globalhealthsciencegroup.com/index.php/IJGHR

THE EFFECT OF TURMERIC LEAF (CURCUMA LONGA L.) EXTRACT ON LEPTIN, HMG-CoA LEVELS, AND BLOOD VESSEL HISTOPATHOLOGY IN HYPERLIPIDEMIC RATS INDUCED BY A HIGH-FAT DIET AND PROPYLTHIOURACIL: AN IN SILICO AND IN VIVO STUDY

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ABSTRACT
Hyperlipidemia is a major cardiovascular risk factor with increasing global prevalence. Turmeric leaves (Curcuma longa L.) contain bioactive compounds with potential antihyperlipidemic properties through modulation of leptin and HMG-CoA reductase. To analyze the effects of ethanolic turmeric leaf extract on leptin, HMG-CoA levels, and blood vessel histopathology in hyperlipidemic rats using in silico and in vivo approaches. Thirty-six male Wistar rats were divided into six groups: normal control (K1), hyperlipidemia control (K2), simvastatin 0.9 mg/kg BW (K3), and turmeric extract at 300 (K4), 600 (K5), and 1200 mg/kg BW (K6). Hyperlipidemia was induced with high-fat diet and propylthiouracil. In silico molecular docking evaluated compound-protein interactions. Phytochemical screening confirmed five bioactive compound classes. In silico analysis showed rutin with strong binding affinities to leptin (−10.2 kcal/mol) and HMG-CoA reductase (−9.8 kcal/mol). The 300 mg/kg dose significantly improved lipid profiles, reduced aortic wall thickness (192.59±6.99 µm), foam cells (24.17±4.31), and HMG-CoA levels (3.45±0.42 ng/mL) ($p<0.001$). The 600 mg/kg dose optimally restored leptin (485.67±62.34 pg/mL). Ethanolic turmeric leaf extract exerts significant antihyperlipidemic effects by improving lipid profiles, attenuating atherosclerosis, and modulating leptin and HMG-CoA reductase.

Keywords: atherosclerosis; curcuma longa; HMG-CoA reductase; hyperlipidemia; leptin; phytochemicals

How to cite (in APA style)
Angie, M., Anto, E. J., & Siahaan, J. M. (2026). The Effect of Turmeric Leaf (Curcuma Longa L.) Extract on Leptin, Hmg-Coa Levels, and Blood Vessel Histopathology in Hyperlipidemic Rats Induced by A High-Fat Diet and Propylthiouracil: An in Silico and in Vivo Study. Indonesian Journal of Global Health Research, 8(3), 1135–1144. https://doi.org/10.37287/ijghr.v8i3.1510.

INTRODUCTION

Hyperlipidemia is a pathological condition characterized by elevated levels of blood lipids, including total cholesterol, triglycerides, and low-density lipoprotein (LDL), accompanied by a reduction in high-density lipoprotein (HDL) (Nelson, 2013). This condition is a major risk factor for the development of cardiovascular diseases, which remain the leading cause of global morbidity and mortality (Poznyak et al., 2020). The prevalence of hyperlipidemia continues to rise in parallel with lifestyle changes and modern dietary patterns that are high in saturated fats and low in dietary fiber (Arnett et al., 2019).

The pathophysiology of hyperlipidemia involves complex molecular mechanisms, including disruption of lipid homeostasis, endothelial dysfunction, and chronic vascular inflammation (Gimbrone & García-Cardeña, 2016). One of the most serious consequences of hyperlipidemia is the formation of atherosclerotic plaques within the vascular wall, mediated by foam cell accumulation and proliferation of vascular smooth muscle cells (Chistiakov et al., 2017). This process reflects intricate interactions among metabolic, hormonal, and inflammatory factors.

Metabolic biomarkers such as leptin and HMG-CoA reductase play critical roles in the regulation of lipid and energy metabolism. Leptin, primarily secreted by adipose tissue, is involved in the regulation of appetite, glucose metabolism, and energy homeostasis through the JAK2/STAT3 pathway (Park & Ahima, 2015; Wauman et al., 2017; Pereira et al., 2021). In hyperlipidemic conditions, leptin resistance and dysregulation contribute to metabolic dysfunction and increased cardiovascular risk (Sáinz et al., 2015). HMG-CoA reductase functions as the rate-limiting enzyme in cholesterol biosynthesis, catalyzing the conversion of HMG-CoA to mevalonate, and represents a primary pharmacological target for cholesterol-lowering statin therapy (Istrate et al., 2020). Understanding the interplay between these metabolic regulators is essential for developing effective therapeutic strategies against hyperlipidemia.

Although statins are widely used and effective in the conventional management of hyperlipidemia, their use is frequently associated with adverse effects such as myopathy, hepatic dysfunction, and drug-drug interactions (Nissen et al., 2016). These limitations have stimulated interest in alternative therapies derived from medicinal plants that offer improved safety profiles and multitarget actions. Curcuma longa L. (turmeric) has long been used in traditional medicine and has been shown to possess antioxidant, anti-inflammatory, and hypolipidemic properties (Prasad & Aggarwal, 2011).

Turmeric leaves contain a variety of bioactive compounds, including flavonoids, alkaloids, saponins, tannins, and phenolic compounds, which have potential therapeutic value in the management of hyperlipidemia (Suryanto, 2009; Awin et al., 2016). Both in vitro and in vivo studies have demonstrated that these compounds can inhibit LDL oxidation, enhance reverse cholesterol transport, and attenuate vascular inflammation (Mahfouz et al., 2009; Gao et al., 2019). However, comprehensive investigations evaluating the effects of turmeric leaves on specific metabolic biomarkers such as leptin and HMG-CoA reductase in hyperlipidemic models remain limited.

Therefore, the present study was designed to address this gap by evaluating the effects of ethanolic turmeric leaf extract on lipid profiles, aortic histopathology, and levels of leptin and HMG-CoA reductase in a hyperlipidemic rat model induced by a high-fat diet (HFD) and propylthiouracil (PTU). Therefore, the present study was designed to address this gap. The primary objective was to evaluate the antihyperlipidemic effects of ethanolic turmeric leaf extract and to elucidate its mechanisms of action through modulation of leptin and HMG-CoA reductase. Specifically, this study investigated the extract's effects on lipid profiles, aortic histopathology, and levels of leptin and HMG-CoA reductase in a hyperlipidemic rat model induced by a high-fat diet (HFD) and propylthiouracil (PTU). Additionally, an in silico molecular docking approach was employed to assess the binding interactions between bioactive compounds in the extract and target proteins (leptin and HMG-CoA reductase), providing mechanistic insight to support the experimental findings.

METHOD

Study Design and Animals

This study employed a laboratory-based experimental design using a post-test randomized controlled group approach. A total of 36 healthy male Wistar rats (*Rattus norvegicus*), aged 2-3 months and weighing 150-200 g, were included. The sample size was determined using Federer's formula (Adiputra et al., 2021), resulting in six rats per group. Animals were randomly allocated into six experimental groups using simple random sampling. All experimental procedures were approved by the Animal Ethics Committee of the Faculty of Medicine, Methodist University of Indonesia (Ethical Clearance No. 045/KEPK-FKUMI/IX/2024).

Hyperlipidemia Induction and Experimental Groups

Hyperlipidemia was induced by administering a high-fat diet (HFD) combined with 0.01% propylthiouracil (PTU) at a dose of 12.5 mg/day in drinking water for four weeks (Untari & Pramukantoro, 2020). Rats were considered hyperlipidemic when total cholesterol levels exceeded 200 mg/dL (Harsa, 2014). The experimental groups consisted of: (K1) normal control group receiving standard diet and water *ad libitum*; (K2) hyperlipidemia control group receiving HFD+PTU; (K3) positive control group receiving HFD+PTU+simvastatin 0.9 mg/kg BW (Wang et al., 2021); and three treatment groups receiving HFD+PTU plus ethanolic turmeric leaf extract at doses of (K4) 300 mg/kg BW, (K5) 600 mg/kg BW, and (K6) 1200 mg/kg BW (Wang et al., 2021).

Preparation of Turmeric Leaf Extract

Fresh turmeric (*Curcuma longa* L.) leaves were collected from local cultivation sites in Medan, North Sumatra, Indonesia, and authenticated by the Herbarium Medanense (MEDA), University of Sumatera Utara. The leaves were washed, dried at room temperature, and ground into powder. The dried powder was extracted using 96% ethanol through maceration for 5 days at room temperature with occasional stirring (Ditjen POM, 1995). The extract was filtered and concentrated using a rotary evaporator at 40°C to obtain a thick extract, which was then stored at 4°C until use.

Phytochemical Screening

Phytochemical screening was performed using standard procedures to identify the presence of flavonoids, alkaloids, saponins, tannins, and phenolic compounds (Widowati et al., 2016, 2017, 2018). Flavonoid identification was performed using the magnesium-HCl reduction test. Alkaloid detection employed Dragendorff's reagent. Saponins were identified through the foam test. Tannins were detected using ferric chloride reagent. Phenolic compounds were identified using the Folin-Ciocalteu method.

Biochemical and Histopathological Assessments

At the end of the treatment period, blood samples were collected via cardiac puncture after overnight fasting. Serum was separated by centrifugation at 3000 rpm for 15 minutes and stored at −20°C until analysis. Lipid profiles (total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol) were measured using enzymatic colorimetric methods with commercial kits (DiaSys Diagnostic Systems, Germany). Leptin levels were quantified using a rat leptin ELISA kit (Elabscience, USA), and HMG-CoA reductase activity was measured using a commercial ELISA kit (MyBioSource, USA) according to the manufacturer's protocols.

Following blood collection, rats were euthanized, and aortic tissues were carefully dissected, fixed in 10% buffered formalin, and processed for histopathological examination. Tissues were embedded in paraffin, sectioned at 5 μm thickness, and stained with hematoxylin-eosin (H&E). Histopathological parameters including aortic lumen diameter, wall thickness, and foam cell count were evaluated using light microscopy (Olympus BX51, Japan) at 400× magnification by a blinded pathologist. Atherosclerotic lesions were classified according to the modified American Heart Association classification scheme (Sakamoto et al., 2018).

In Silico Molecular Docking Analysis

Molecular docking studies were conducted to evaluate the binding affinities of major bioactive compounds in turmeric leaves to target proteins (Pagadala et al., 2017). Three-dimensional structures of leptin (PDB ID: 8AVC) and HMG-CoA reductase (PDB ID: 1HW9) were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). Ligand structures (curcumin, demethoxycurcumin, bisdemethoxycurcumin, rutin, quercetin, and kaempferol) were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and optimized using MarvinSketch 21.14.

Protein preparation involved removal of water molecules and heteroatoms, addition of polar hydrogen atoms, and energy minimization using YASARA software. Molecular docking was

performed using Molegro Virtual Docker 6.0 with the MolDock scoring function (Purnomo, 2012). The binding site was defined based on cavity detection algorithms. Docking simulations were run with default parameters, generating 10 poses per ligand. The best pose for each compound was selected based on the MolDock score and visual inspection of binding interactions. Validation was performed by re-docking the native ligand and calculating the root mean square deviation (RMSD). Visualization of protein-ligand interactions was performed using Discovery Studio Visualizer 2021.

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene's test. Differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by Scheffé post hoc testing for multiple comparisons. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA).

RESULT

Phytochemical Composition and In Silico Analysis

Phytochemical screening confirmed the presence of flavonoids, alkaloids, saponins, tannins, and phenolic compounds in the ethanolic turmeric leaf extract (Table 1). These findings are consistent with previous reports on the phytochemical composition of *Curcuma longa* leaves (Suryanto, 2009; Dosoky & Setzer, 2018). *In silico* molecular docking analysis demonstrated that rutin exhibited the highest binding affinity toward leptin with a binding score of −10.2 kcal/mol and toward HMG-CoA reductase with −9.8 kcal/mol. Other flavonoids including quercetin and kaempferol also showed favorable binding energies ranging from −8.5 to −9.1 kcal/mol. Curcuminoids displayed moderate binding affinities (−7.2 to −8.3 kcal/mol). These substantially negative binding scores indicate energetically stable interactions and suggest potential for biological activity.

Table 1.

Phytochemical Screening of Ethanolic Turmeric (Curcuma longa) Leaf Extract

Bioactive Compound	Result
Flavonoids	+
Alkaloids	+
Saponins	+
Tannins	+
Phenolic Compounds	+

Note. (+) indicates a positive result for the presence of bioactive compounds.

Effects on Lipid Profile

Administration of the ethanolic turmeric leaf extract resulted in significant improvements in lipid profile parameters (Table 2). The hyperlipidemia control group (K2) exhibited markedly elevated levels of total cholesterol (210.50 ± 2.74 mg/dL), triglycerides (246.83 ± 8.47 mg/dL), and LDL cholesterol (96.33 ± 5.68 mg/dL), with reduced HDL cholesterol (65.00 ± 3.74 mg/dL) compared to the normal control group (K1). The positive control group (K3) treated with simvastatin demonstrated significant reductions in total cholesterol (181.67 ± 6.98 mg/dL), triglycerides (179.17 ± 8.80 mg/dL), and LDL cholesterol (70.17 ± 8.11 mg/dL), along with an increase in HDL cholesterol (75.67 ± 1.97 mg/dL) ($p < 0.001$).

Among the turmeric leaf extract-treated groups, K4 (300 mg/kg BW) exhibited the most favorable outcomes, with lipid parameters approaching those of the simvastatin group. Total cholesterol was reduced to 184.50 ± 7.09 mg/dL, triglycerides to 183.67 ± 9.56 mg/dL, and LDL cholesterol to 71.50 ± 6.75 mg/dL, while HDL cholesterol increased to 76.17 ± 2.23 mg/dL ($p < 0.001$). The K5 (600 mg/kg BW) and K6 (1200 mg/kg BW) groups also showed significant improvements compared to the hyperlipidemia control, although the magnitude of change was less pronounced than in the K4 group. These findings indicate a dose-dependent pattern with optimal lipid-lowering effects at the 300 mg/kg BW dose.

Table 2.
Lipid Profile After Treatment with Ethanolic Turmeric Leaf Extract

Group	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
K1 (Normal)	145.33 ± 5.12	98.17 ± 7.23	45.67 ± 4.21	80.50 ± 3.12
K2 (Hyperlipidemia)	210.50 ± 2.74	246.83 ± 8.47	96.33 ± 5.68	65.00 ± 3.74
K3 (Simvastatin)	181.67 ± 6.98	179.17 ± 8.80	70.17 ± 8.11	75.67 ± 1.97
K4 (300 mg/kg)	184.50 ± 7.09	183.67 ± 9.56	71.50 ± 6.75	76.17 ± 2.23
K5 (600 mg/kg)	192.33 ± 8.45	198.50 ± 10.23	78.67 ± 7.89	73.50 ± 2.85
K6 (1200 mg/kg)	198.67 ± 9.12	205.83 ± 11.67	82.33 ± 8.45	71.83 ± 3.21

Note. Data presented as mean ± SD. $p < 0.001$ for all lipid parameters determined by one-way ANOVA followed by Scheffé post hoc test.

Effects on Aortic Histopathology

Aortic histopathological analysis revealed significant differences in lumen diameter, aortic wall thickness, and foam cell count among the experimental groups (Table 3). The hyperlipidemia control group (K2) exhibited a marked reduction in lumen diameter (382.50 ± 15.67 μm), an increase in aortic wall thickness (232.67 ± 8.09 μm), and substantial accumulation of foam cells (42.50 ± 5.24) compared with the normal control group ($p < 0.001$). These findings are characteristic of early atherosclerotic lesion development (Sakamoto et al., 2018).

Treatment with simvastatin (K3) resulted in significant improvement, with a lumen diameter of 435.83 ± 11.28 μm, aortic wall thickness of 192.59 ± 6.99 μm, and foam cell count of 24.17 ± 4.31 ($p < 0.001$ vs. K2). Among the extract-treated groups, K4 (300 mg/kg BW) demonstrated the most favorable histopathological outcomes, with parameters approaching those of the simvastatin group: lumen diameter 428.67 ± 13.54 μm, wall thickness 196.33 ± 7.45 μm, and foam cell count 26.50 ± 4.76. Higher doses (K5 and K6) also showed significant improvements compared to the hyperlipidemia control, though less pronounced than the 300 mg/kg dose. Histopathological examination using H&E staining revealed reduced lipid accumulation, decreased inflammatory cell infiltration, and preservation of vascular architecture in the treatment groups.

Table 3.
Aortic Histopathological Parameters After Treatment

Group	Lumen Diameter (μm)	Wall Thickness (μm)	Foam Cell Count
K1 (Normal)	445.67 ± 12.34	178.33 ± 5.67	18.50 ± 3.21
K2 (Hyperlipidemia)	382.50 ± 15.67	232.67 ± 8.09	42.50 ± 5.24
K3 (Simvastatin)	435.83 ± 11.28	192.59 ± 6.99	24.17 ± 4.31
K4 (300 mg/kg)	428.67 ± 13.54	196.33 ± 7.45	26.50 ± 4.76
K5 (600 mg/kg)	415.50 ± 14.89	205.67 ± 8.23	30.83 ± 5.12
K6 (1200 mg/kg)	408.33 ± 16.45	212.50 ± 9.67	34.17 ± 5.89

Note. Data presented as mean ± SD. $p < 0.001$ for all histopathological parameters determined by one-way ANOVA followed by Scheffé post hoc test.

Effects on Metabolic Biomarkers

Measurement of metabolic biomarkers revealed significant differences among groups for both leptin and HMG-CoA reductase levels (Table 4). Leptin levels were markedly decreased in the hyperlipidemia control group (287.33 ± 56.48 pg/mL) compared with the normal control group (628.45 ± 74.22 pg/mL) ($p < 0.001$). This reduction reflects the metabolic dysfunction associated with hyperlipidemia and is consistent with previous reports of leptin dysregulation in metabolic disorders (Pan et al., 2022; Pereira et al., 2021).

Administration of turmeric leaf extract increased leptin levels in a dose-dependent manner. The K5 group (600 mg/kg BW) showed the most pronounced increase (485.67 ± 62.34 pg/mL),

approaching normal values and exceeding those observed in the simvastatin group (456.78 ± 68.34 pg/mL) ($p < 0.001$ vs. K2). The K4 group (300 mg/kg BW) also demonstrated significant leptin restoration (425.33 ± 58.92 pg/mL), while the highest dose (K6) resulted in intermediate values (445.83 ± 65.78 pg/mL).

HMG-CoA reductase activity, the rate-limiting enzyme in cholesterol biosynthesis (Miziorko, 2011), was significantly elevated in the hyperlipidemia control group (8.76 ± 1.23 ng/mL) compared with the normal group (2.34 ± 0.45 ng/mL) ($p < 0.001$). The K4 group exhibited the greatest reduction in HMG-CoA reductase activity (3.45 ± 0.42 ng/mL), surpassing the simvastatin group (4.12 ± 0.58 ng/mL) and approaching normal values ($p < 0.001$ vs. K2). This finding is particularly noteworthy as it demonstrates comparable efficacy to the standard statin therapy. The K5 and K6 groups demonstrated intermediate HMG-CoA reductase levels of 4.67 ± 0.73 ng/mL and 5.23 ± 0.89 ng/mL, respectively, both significantly lower than the hyperlipidemia control ($p < 0.001$).

Table 4.
Levels of Leptin and HMG-CoA Reductase After Treatment

Group	Leptin (pg/mL)	HMG-CoA Reductase (ng/mL)
K1 (Normal)	628.45 ± 74.22	2.34 ± 0.45
K2 (Hyperlipidemia)	287.33 ± 56.48	8.76 ± 1.23
K3 (Simvastatin)	456.78 ± 68.34	4.12 ± 0.58
K4 (300 mg/kg)	425.33 ± 58.92	3.45 ± 0.42
K5 (600 mg/kg)	485.67 ± 62.34	4.67 ± 0.73
K6 (1200 mg/kg)	445.83 ± 65.78	5.23 ± 0.89

Note. Data presented as mean ± SD. $p < 0.001$ for both leptin and HMG-CoA reductase determined by one-way ANOVA followed by Scheffé post hoc test.

DISCUSSION

This study provides comprehensive evidence of the therapeutic effects of ethanolic turmeric leaf extract in ameliorating hyperlipidemia and modulating metabolic biomarkers. The principal contribution of this research lies in demonstrating the multitarget effects of turmeric leaves in improving lipid profiles, reducing atherosclerosis, and simultaneously modulating the metabolic biomarkers leptin and HMG-CoA reductase in a clinically relevant hyperlipidemia model. These findings extend previous knowledge on *Curcuma longa*'s therapeutic potential beyond its traditional uses (Fuloria et al., 2022).

Antihyperlipidemic Effects and Molecular Mechanisms

The significant improvement in lipid profiles observed in this study is consistent with previous reports describing the hypolipidemic effects of curcumin and other bioactive compounds in turmeric (Qin et al., 2017). Reductions in total cholesterol, triglycerides, and LDL cholesterol, accompanied by increased HDL cholesterol levels in the treatment groups, may be explained by multiple molecular mechanisms. Flavonoids present in the extract, particularly rutin identified through *in silico* analysis, may inhibit cholesterol synthesis by regulating the expression of HMG-CoA reductase and enhancing hepatic LDL receptor expression (Tien et al., 2023).

The finding that a dose of 300 mg/kg BW exerted optimal effects on lipid profiles and HMG-CoA inhibition, approaching the efficacy of simvastatin, suggests a high therapeutic potential. This phenomenon may be explained by the concept of hormesis, wherein moderate doses optimally activate adaptive pathways, while higher doses may trigger compensatory mechanisms that reduce efficacy (Calabrese, 2021. The superior HMG-CoA reductase inhibition at the 300 mg/kg dose provides mechanistic support for the observed lipid-lowering effects and aligns with the *in silico* findings showing strong binding affinity of rutin to HMG-CoA reductase.

Modulation of Leptin and Metabolic Homeostasis

The reduction of leptin levels under hyperlipidemic conditions and their subsequent increase following turmeric leaf extract treatment represents a novel and noteworthy finding. Leptin plays a

crucial role in appetite regulation and energy metabolism through the JAK2/STAT3 pathway (Park & Ahima, 2015; Wauman et al., 2017), and its suppression in hyperlipidemia may reflect dysregulated metabolic homeostasis. The observed leptin dysregulation in the hyperlipidemia control group is consistent with findings reported by Pan et al. (2022) in their study of plant extracts' effects on metabolic pathways.

Restoration of leptin levels following treatment suggests normalization of metabolic signaling. The dose-dependent increase in leptin levels, with optimal restoration at 600 mg/kg BW, suggests that this dose may be more effective in modulating leptin signaling pathways. The elevation of leptin levels in the treatment groups may contribute to improved lipid metabolism through multiple mechanisms, including enhanced fatty acid oxidation, reduced lipogenesis, and improved insulin sensitivity (Minokoshi et al., 2002). Leptin's anti-inflammatory effects may also contribute to the observed improvements in vascular health (Martínez-Sánchez, 2020).

Antiatherosclerotic Effects

The significant reduction in aortic wall thickness and foam cell count in the treatment groups demonstrates the antiatherosclerotic potential of turmeric leaf extract. A decrease in foam cell accumulation indicates inhibition of atherosclerotic progression, a hallmark of plaque formation (Chistiakov et al., 2017). Foam cells, derived from lipid-laden macrophages, are a key histological feature of atherosclerosis (Sakamoto et al., 2018). Their reduction suggests that the extract may inhibit LDL oxidation, reduce macrophage lipid uptake, or enhance cholesterol efflux from foam cells.

The antiatherosclerotic effects are likely mediated through the antioxidant and anti-inflammatory properties of the extract's bioactive compounds. Flavonoids and phenolic compounds can inhibit LDL oxidation through free radical scavenging and metal ion chelation (Mahfouz et al., 2009). Curcuminoids present in *Curcuma longa* have been reported to prevent LDL oxidation and reduce foam cell formation (Gao et al., 2019). Suppression of vascular inflammation via modulation of NF-κB signaling and proinflammatory cytokines may further contribute to attenuation of atherosclerotic lesions (Chainani-Wu, 2003). The improvement in aortic histopathology correlates well with the favorable changes in lipid profiles and metabolic biomarkers, suggesting a coordinated therapeutic effect.

Relevance of In Silico Findings

Molecular docking analysis demonstrated that rutin, a major flavonoid in the extract, exhibited favorable binding affinities toward both leptin and HMG-CoA reductase. The substantially negative binding scores (−10.2 kcal/mol for leptin and −9.8 kcal/mol for HMG-CoA reductase) indicate energetically stable interactions (Pagadala et al., 2017). These *in silico* findings provide mechanistic support for the biological effects observed *in vivo*, suggesting that rutin may act as a dual modulator of leptin signaling and cholesterol biosynthesis.

The strong binding affinity to HMG-CoA reductase provides a molecular basis for the observed inhibition of this enzyme and the resultant lipid-lowering effects, similar to the mechanism of action of statins (Wang et al., 2023). Similarly, the interaction with leptin may contribute to the restoration of leptin levels and improved metabolic homeostasis. However, it is important to note that *in silico* predictions should be validated through further *in vitro* binding studies and mechanistic investigations to confirm direct molecular interactions.

Clinical Implications and Future Perspectives

The findings of this study have important translational implications. Turmeric leaf extract may be developed as an adjunctive or alternative therapy for hyperlipidemia, particularly for patients who are intolerant to statins or experience adverse effects (Nissen et al., 2016). Its multitarget effects—addressing lipid profiles, metabolic biomarkers, and atherosclerosis—offer a promising holistic

therapeutic approach. The demonstration of HMG-CoA reductase inhibition comparable to simvastatin, combined with beneficial effects on leptin and vascular health, positions turmeric leaf extract as a potential natural statin alternative with additional metabolic benefits.

Study Limitations

Several limitations should be acknowledged. Although the high-fat diet and PTU-induced hyperlipidemia model is relevant, it does not fully replicate the complexity of human hyperlipidemia, which is often influenced by genetic factors and comorbidities. The relatively short observation period may not capture long-term therapeutic effects. Future studies should explore chronic administration, long-term safety, and potential interactions with conventional lipid-lowering drugs. Additionally, pharmacokinetic studies assessing absorption, distribution, metabolism, and excretion of bioactive compounds would provide critical insights for dose optimization and clinical translation.

CONCLUSION

Ethanolic turmeric (Curcuma longa L.) leaf extract exhibits significant antihyperlipidemic effects by improving lipid profiles, reducing atherosclerosis, and modulating the metabolic biomarkers leptin and HMG-CoA reductase in a hyperlipidemic rat model. A dose of 300 mg/kg BW was the most effective in improving lipid profiles, inhibiting HMG-CoA reductase, and reducing atherosclerotic changes, while a dose of 600 mg/kg BW was optimal for leptin restoration. In silico analyses support the potential molecular interactions between bioactive compounds, particularly rutin, and target proteins. These findings provide scientific evidence for the development of turmeric leaf extract as a natural therapeutic agent for hyperlipidemia management, offering a multitarget approach that addresses both lipid metabolism and metabolic homeostasis.

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