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RESEARCH **Open Access**

Dose-Dependent Effect of Ethanol Extract of Red Ginger (Zingiber officinale var. rubrum) on Total Cholesterol Levels in Hypercholesterolemic Mice: An Experimental Study

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Abstract
Cholesterol is an essential lipid in the body; however, excessive levels may lead to hypercholesterolemia and increase the risk of coronary heart disease. Natural alternatives such as red ginger extract (Zingiber officinale var. rubrum) have potential due to their antioxidant and anti-inflammatory properties. This study aimed to evaluate the effect and determine the optimal dose of red ginger extract in reducing total cholesterol levels. A laboratory experimental study with a pre-test and post-test control group design was conducted using 30 male mice (Mus musculus), which were randomly divided into five groups (three treatment groups and two control groups). The treatment groups received different doses of red ginger ethanol extract. The results showed that administration of red ginger extract reduced total cholesterol levels in mice, with mean total cholesterol level decreased from 163.57 mg/dL to 131.87 mg/dL. Statistical analysis indicated a significant reduction in cholesterol levels, and differences were observed among treatment groups. The highest dose (18 mg/kg body weight) demonstrated the most optimal effect. In conclusion, red ginger ethanol extract effectively reduces total cholesterol levels in mice, with higher doses showing greater efficacy.

Keywords: Red Ginger, Total Cholesterol, Hypercholesterolemia, Mice, Ethanol Extract.

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1. INTRODUCTION

Hypercholesterolemia remains a major public health concern because of its close association with cardiovascular disease, the leading cause of death worldwide. According to the World Health Organization, cardiovascular diseases account for approximately 17.9 million deaths annually (Ghodeshwar et al., 2023). Over the past five years, global data indicate a rising trend in the prevalence of hypercholesterolemia and dyslipidemia, particularly in low- and middle-income countries, partly because of urbanization, unhealthy dietary patterns, and sedentary lifestyles (Ibrahim, 2025).

In Indonesia, hypercholesterolemia and other lipid metabolism disorders remain important public health concerns. Data from the Indonesian Health Survey 2023 showed that metabolic risk factors associated with cardiovascular disease continue to increase, including central obesity, diabetes, and dyslipidemia-related abnormalities. The prevalence of high and very high triglyceride levels increased from 11.9% in 2013 to 23.9% in 2023, while low High-Density Lipoprotein (HDL) levels also showed an increasing trend, indicating a persistent burden of dyslipidemia among the Indonesian population (Nasution et al., 2026). Furthermore, cardiovascular disease remains one of the leading causes of morbidity and mortality in Indonesia, highlighting the growing impact of metabolic disorders on national health outcomes (Indonesia, 2023). These findings emphasize the urgent need for effective, safe, and sustainable strategies for cholesterol control and cardiovascular disease prevention, including the exploration of plant-based therapeutic approaches (Christina et al., 2025).

Given this growing burden, the exploration of natural-based therapies has gained increasing attention (Anand et al., 2026). Although statins are widely used and effective in lowering cholesterol levels, their long-term use may be associated with side effects, leading to interest in alternative approaches (Koppula et al., 2025).

Red ginger (Zingiber officinale var. rubrum) is one of the medicinal plants that has attracted considerable attention for its lipid-lowering potential. Compared with other ginger varieties, such as white ginger (Zingiber officinale var. officinale) and small white ginger (Zingiber officinale var. amarum), red ginger contains relatively higher concentrations of bioactive compounds, particularly gingerols, shogaols, flavonoids, and phenolic substances, which contribute to its stronger antioxidant and pharmacological activities (Herlina et al., 2025; Supu et al., 2018). Previous studies have demonstrated that red ginger is effective in improving lipid profiles by reducing total cholesterol, low-density lipoprotein (LDL), and triglyceride levels while increasing high-density lipoprotein (HDL) concentrations (Gumbarewicz et al., 2022; Puspitasari et al., 2025; Salih et al., 2023). These effects are comparable to or greater than those reported for several other medicinal plants commonly used in dyslipidemia management, including garlic, turmeric, and coriander, making red ginger a promising candidate for the development of plant-based hypolipidemic therapies. The bioactive compounds present in red ginger exhibit antioxidant and anti-inflammatory properties that may inhibit lipid peroxidation, reduce oxidative stress, and prevent LDL oxidation, which are critical processes in the pathogenesis of atherosclerosis (Gianazza et al., 2021; Xuan et al., 2023). Furthermore, its anti-inflammatory activity may contribute to improved lipid metabolism and protection against vascular damage associated with hypercholesterolemia.

Previous studies have shown that red ginger extract can reduce total cholesterol, LDL, and triglyceride levels, and may increase HDL levels in experimental models (Gumbarewicz et al., 2022; Puspitasari et al., 2025; Salih et al., 2023). However, most studies focus on general efficacy, and comparative evidence regarding its effectiveness across different doses is still limited.

Although the lipid-lowering effects of ginger have been studied, evidence on the effective dose of red ginger ethanol extract remains limited, particularly in controlled experimental models. This gap is important as it helps identify the level at which therapeutic benefit is maximized while unnecessary exposure is minimized.. Therefore, this study aims to evaluate the effect of ethanol extract of red ginger (Zingiber officinale var. rubrum) on total cholesterol levels in hypercholesterolemic mice (Mus musculus) and to identify the dose associated with the greatest cholesterol-lowering response.

2. RESEARCH METHOD

This laboratory experimental study used a pre-test and post-test control group design to assess the effect of red ginger (Zingiber officinale var. rubrum) ethanol extract on total cholesterol levels in mice (Mus musculus). The study was conducted at the Laboratory of the Faculty of Medicine, Universitas Muslim Indonesia.

Thirty male mice aged 6–8 weeks and weighing 25–30 grams were included. The sample size was determined using Federer's formula, with five groups consisting of three treatment groups and two control groups, each containing six mice to anticipate potential dropouts. The mice were randomly assigned into the groups using a simple randomization method.

Hypercholesterolemia was induced by administering a high-fat diet in the form of raw chicken egg yolk at a dose of 0.5 mL/day orally for 14 days to increase cholesterol levels above 130 mg/dL. After successful induction, the mice were assigned to five groups: a negative control group receiving a standard diet, a positive control group receiving simvastatin, and three treatment groups receiving red ginger ethanol extract at doses of 6 mg/kg body weight, 12 mg/kg body weight, and 18 mg/kg body weight, respectively. All interventions were administered orally once daily for 14 consecutive days.

The independent variable in this study was the administration of red ginger ethanol extract, while the dependent variable was total cholesterol level. Inclusion criteria included healthy, active male mice without physical abnormalities and with cholesterol levels above 130 mg/dL after induction. Exclusion criteria included mice that died during the study or experienced significant weight loss. The equipment used in this study included a blender, analytical balance, measuring cylinders, rotary evaporator, and GCU meter, while the materials included red ginger, 96% ethanol, standard feed, distilled water, simvastatin, egg yolk, and cholesterol test strips.

Total cholesterol levels were measured before and after treatment. The data were analyzed using SPSS software. Statistical analysis included the Shapiro–Wilk test for normality and Levene's test for homogeneity, followed by non-parametric tests, including the Wilcoxon signed-rank test, Kruskal–Wallis test, and Mann–Whitney post hoc test to assess differences within and between groups. This study has received ethical approval from the Health Research Ethics Committee of Universitas Muslim Indonesia with ethical clearance number UMI012406369.

3. RESULTS AND DISCUSSION

Table 1. Total Cholesterol Levels of Mice at Three Measurement Phases (mg/dL)

Phase	**Group 1 (6 mg/kg)**	**Group 2 (12 mg/kg)**	**Group 3 (18 mg/kg)**	**Positive Control**	**Negative Control**
Baseline Measurement (Mean ± SD)	98.0 ± 7.8	96.0 ± 10.3	95.7 ± 9.9	95.5 ± 9.2	94.0 ± 8.3
Post-Induction Measurement	153.8 ± 6.7	172.2 ± 6.7	189.3 ± 4.5	154.3 ± 8.2	148.2 ± 6.1
Post-Treatment Measurement	134.0 ± 5.2	121.0 ± 8.8	105.8 ± 3.8	91.7 ± 13.7	206.8 ± 5.5

Table 1 shows that baseline cholesterol levels were relatively similar across all groups, indicating homogeneous initial conditions. After high-fat diet induction, cholesterol levels increased markedly in all groups, confirming successful hypercholesterolemia induction. Following treatment, cholesterol levels decreased in all treatment groups, with the greatest reduction observed in Group 3 (18 mg/kg body weight). The Positive control group also showed a substantial decrease, while the Negative control group exhibited a further increase in cholesterol levels. The trend of cholesterol changes across all groups is illustrated in Figure 1.

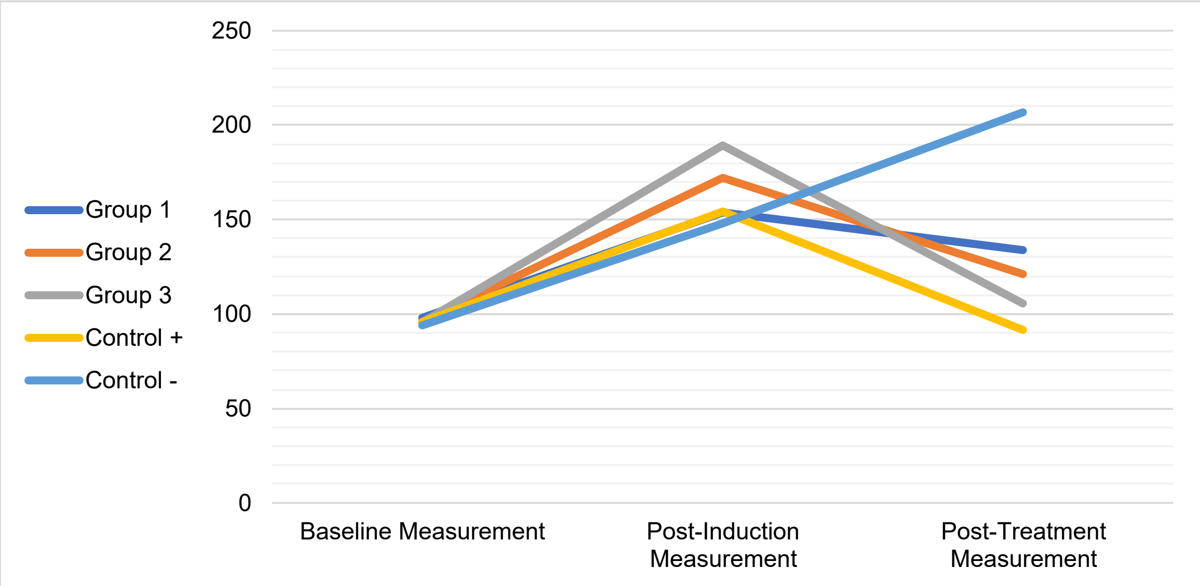

Figure 1. Mean total cholesterol levels across experimental groups.

The results showed that administration of red ginger ethanol extract significantly reduced total cholesterol levels in mice. A dose-dependent effect was observed, where higher doses resulted in greater reductions in cholesterol levels. The trend of cholesterol changes across all experimental groups is illustrated in Figure 1. The figure clearly shows that cholesterol levels increased after high-fat diet induction and subsequently decreased following treatment, particularly in the higher dose groups. Group 3 (18 mg/kg body weight) demonstrated the most substantial reduction, approaching the effect observed in the positive control group (simvastatin). In contrast, the negative control group showed a continuous increase in cholesterol levels, indicating the absence of therapeutic intervention.

Table 2. Descriptive statistics and normality test.

Variable	**N**	**Mean (mg/dL)**	**SD**	**Shapiro–Wilk (p-value)**
Pre-test	30	163.57	16.61	0.028
Post-test	30	131.87	41.59	<0.001

The mean cholesterol level decreased from 163.57 ± 16.61 mg/dL to 131.87 ± 41.59 mg/dL, indicating an overall reduction after treatment. The Shapiro–Wilk test showed non-normal data distribution ($p < 0.05$), justifying the use of non-parametric tests.

Table 3. Homogeneity and wilcoxon signed-rank test

Analysis	**N**	**p-value**	**Interpretation**
Levene's Test	30	0.446	Homogeneous variance ($p > 0.05$)
Wilcoxon Test	30	0.007	Significant difference

The Wilcoxon test confirmed a significant reduction in cholesterol levels after treatment ($p < 0.05$).

Table 4. Kruskal–wallis test.

Group	N	Mean Rank	p-value
Group 1	6	20.92	<0.001
Group 2	6	16.00	
Group 3	6	8.42	
Positive Control	6	4.67	
Negative Control	6	27.50	

The Kruskal–Wallis test showed a significant difference among groups, indicating that treatment variation influenced cholesterol reduction.

Table 5. Mann-whitney post hoc test (p-values).

Comparison	p-value
G1 vs G2	0.019
G1 vs G3	0.004
G1 vs Positive Control	0.004
G1 vs Negative Control	0.004
G2 vs G3	0.005
G2 vs Positive Control	0.004
G2 vs Negative Control	0.004
G3 vs Positive Control	0.076 (ns)
G3 vs Negative Control	0.004
Positive vs Negative Control	0.004

ns = not significant

Most comparisons showed significant differences ($p < 0.05$), except between Group 3 and the Positive control.

This study found that ethanol extract of red ginger (*Zingiber officinale* var. *rubrum*) significantly reduced total cholesterol levels in hypercholesterolemic mice, with a clear dose-dependent response. Among the tested doses, 18 mg/kg body weight produced the greatest cholesterol-lowering effect and showed no statistically significant difference compared with simvastatin treatment ($p > 0.05$). These findings indicate that red ginger extract possesses substantial hypocholesterolemic activity and that increasing the administered dose enhances its therapeutic efficacy. The observed reduction in cholesterol levels supports previous evidence indicating that ginger supplementation can improve lipid profiles by reducing total cholesterol, low-density lipoprotein (LDL), and triglyceride concentrations while potentially increasing high-density lipoprotein (HDL) levels (Gumbarewicz et al., 2022; Puspitasari et al., 2025; Salih et al., 2023).

The cholesterol-lowering effect observed in this study is likely associated with the rich phytochemical composition of red ginger. Red ginger contains several bioactive compounds, including gingerols, shogaols, paradols, zingerone, flavonoids, and phenolic compounds, which exert antioxidant, anti-inflammatory, and lipid-modulating effects. Compared with other ginger varieties, red ginger has been reported to contain the highest phenolic content and antioxidant activity, indicating a greater concentration of biologically active compounds that may contribute to its stronger therapeutic potential (Ayustaningwarno et al., 2024). In addition, red ginger contains higher levels of essential oils and bioactive constituents, particularly monoterpenoids and phenolic compounds, compared with common ginger varieties, which may enhance its pharmacological activity (Ayustaningwarno et al., 2024; Herlina et al., 2025). These compounds play important roles in reducing oxidative stress, inhibiting lipid peroxidation, suppressing inflammatory pathways, and regulating lipid metabolism, thereby contributing to cholesterol reduction and cardiovascular protection (Garza-Cadena et al., 2023). The superior antioxidant capacity of red ginger is particularly important because oxidative stress and LDL oxidation are major mechanisms involved in the development of atherosclerosis and hypercholesterolemia-related cardiovascular diseases.

These compounds may act synergistically to regulate cholesterol metabolism through multiple pathways. One proposed mechanism involves inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key enzyme responsible for endogenous cholesterol synthesis. Suppression of this enzyme reduces hepatic cholesterol production, thereby lowering circulating cholesterol concentrations (Azizidoost et al., 2019; Lei et al., 2014). In addition, ginger-derived compounds have been reported to increase fecal sterol excretion and bile acid elimination, further contributing to cholesterol reduction (Crichton et al., 2023).

Another important mechanism relates to the antioxidant properties of red ginger. Hypercholesterolemia is strongly associated with oxidative stress, which promotes lipid peroxidation and oxidation of LDL particles (Canbay et al., 2024). Oxidized LDL plays a central role in endothelial dysfunction and atherosclerotic plaque formation (Gianazza et al., 2021). Gingerol and shogaol possess potent free-radical scavenging activity, enabling them to reduce oxidative damage and protect vascular tissues. By decreasing oxidative stress, red ginger may not only lower cholesterol levels but also reduce the progression of atherosclerosis and other cardiovascular complications. This mechanism is particularly relevant because cardiovascular disease remains the leading cause of mortality worldwide, accounting for nearly 18 million deaths annually (Ghodeshwar et al., 2023).

The dose-dependent pattern observed in this study suggests that greater concentrations of bioactive compounds produce stronger biological responses. Mice receiving 18 mg/kg body weight experienced the largest reduction in cholesterol levels, indicating that higher doses provide more effective modulation of lipid metabolism. Similar findings have been reported in recent experimental studies. Herlina et al., (2025) demonstrated that red ginger extract significantly improved lipid profiles and exerted cardioprotective effects in atherosclerotic rats. Likewise, Gumbarewicz et al., (2022) concluded that ginger supplementation consistently improved metabolic syndrome parameters, including dyslipidemia, in animal models. The consistency of these findings strengthens the evidence supporting red ginger as a promising natural hypolipidemic agent.

Beyond its antioxidant effects, red ginger may influence lipid metabolism through anti-inflammatory pathways (Ayustaningwarno et al., 2024; Rampengan et al., 2024). Chronic low-grade inflammation is recognized as a major contributor to dyslipidemia and atherosclerosis (Cifuentes et al., 2024). Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can disrupt lipid homeostasis and accelerate plaque development (Song et al., 2022; Tsioufis et al., 2022). Ginger bioactive compounds have been shown to suppress inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB), thereby reducing inflammatory responses and improving lipid regulation (Xuan et al., 2023). This anti-inflammatory action may partly explain the substantial cholesterol reduction observed in the higher-dose treatment groups.

An important finding of the present study is the absence of a significant difference between the highest dose of red ginger extract and simvastatin. Simvastatin is widely regarded as one of the standard pharmacological therapies for hypercholesterolemia because of its proven efficacy in reducing cardiovascular risk. The comparable performance of red ginger extract suggests that this herbal intervention may have potential as an adjunctive or complementary therapy. Recent studies have shown that combining ginger-derived compounds with conventional lipid-lowering drugs may enhance therapeutic effectiveness while potentially reducing the required dosage of statins (Abdelhamid et al., 2024). Such findings are clinically relevant because prolonged statin use may be associated with adverse effects, including myopathy, hepatotoxicity, and reduced patient adherence in some individuals.

The strong cholesterol reduction observed in this study may also be influenced by the experimental model employed (Van Bennekum et al., 2005). Hypercholesterolemia induction using egg yolk successfully elevated cholesterol concentrations above normal physiological levels, creating a suitable model for evaluating lipid-lowering interventions (Hannah et al., 2023). The controlled administration of extract doses and standardized treatment duration may have contributed to the clear dose-response relationship observed (Sethi et al., 2025). Furthermore, the use of a positive control group enabled direct comparison with a standard therapeutic agent, strengthening the validity of the findings.

From a public health perspective, these findings have important implications. The prevalence of hypercholesterolemia and cardiovascular disease continues to increase in Indonesia and globally, largely due to urbanization, unhealthy dietary patterns, reduced physical activity, and other lifestyle-related factors (Erlinawati, 2025; Nsabimana et al., 2024; Sigit et al., 2022). The identification of affordable and locally available medicinal plants with lipid-lowering properties may contribute to preventive healthcare strategies. Red ginger is widely cultivated and traditionally used in Indonesia, making it an accessible candidate for the development of functional foods, nutraceuticals, or phytopharmaceutical products aimed at cardiovascular disease prevention (Kurniawan, 2025).

Despite these promising findings, several limitations should be acknowledged. First, the sample size was relatively small, which may limit the statistical power and generalizability of the results. Second, only total cholesterol levels were evaluated, whereas other lipid parameters such as LDL, HDL, triglycerides, and very-low-density lipoprotein (VLDL) were not measured. Assessment of these additional biomarkers would provide a more comprehensive understanding of the extract's effects on lipid metabolism. Third, the treatment duration was relatively short and may not fully reflect the long-term efficacy and safety of red ginger supplementation. Finally, because this study was conducted in an animal model, caution should be exercised when extrapolating the findings directly to humans. Future studies should include longer intervention periods, larger sample sizes, detailed lipid profile assessments, molecular investigations of the underlying mechanisms, and randomized clinical trials in human subjects.

Overall, the findings provide further evidence that red ginger ethanol extract possesses significant cholesterol-lowering activity and may represent a promising natural approach for managing hypercholesterolemia. The dose-dependent response observed in this study, together with the comparable efficacy of the highest dose to simvastatin, supports further investigation into its development as a complementary or alternative therapeutic option for cardiovascular disease prevention and lipid management.

4. CONCLUSION

This study demonstrates that the ethanol extract of red ginger (Zingiber officinale var. rubrum) has a significant hypocholesterolemic effect in mice. A clear dose response relationship was observed, with the highest dose (18 mg/kg body weight) showing the most optimal reduction in total cholesterol levels and a comparable effect to the positive control (simvastatin). These findings indicate that red ginger extract is an effective natural agent for lowering cholesterol levels. The results of this study provide important implications for the development of plant-based therapies as alternative or complementary approaches in managing hypercholesterolemia. Given its bioactive compounds and relatively low risk of side effects, red ginger has the potential to be further developed into a functional or therapeutic agent for long-term cholesterol control. However, several limitations should be considered. This study was conducted on animal models with a relatively short duration and limited lipid parameters. Therefore, further studies are recommended to evaluate the long-term safety, effectiveness, and mechanism of action of red ginger extract. Future research should also include comprehensive lipid profile analysis (LDL, HDL, triglycerides) and clinical trials in humans to confirm its applicability in medical practice.

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