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Cardioprotective Effects of Red Ginger Extracted Using Natural Deep Eutectic Solvent on Lipid Profile in Atherosclerotic Rats

Efek Kardioprotektif Ekstrak Jahe Merah dengan Pelarut Natural Deep Eutectic terhadap Profil Lipid pada Tikus Aterosklerosis

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ABSTRACT

Atherosclerosis, a leading cause of cardiovascular disease, is closely related to dyslipidemia. This study evaluated the cardioprotective effects of red ginger (*Zingiber officinale* var. *rubrum*) extracted using a Natural Deep Eutectic Solvent (NADES) on lipid profiles and the risk of atherosclerosis in rats induced with an atherogenic diet and lipopolysaccharide (LPS). Thirty male Sprague-Dawley rats were divided into five groups: normal control, negative control, positive control (Simvastatin), and two treatment groups receiving red ginger extract at 25 mg/kg and 50 mg/kg body weight (BW). After 24 days of treatment, the 25 mg/kg BW dose significantly reduced total and LDL cholesterol while increasing HDL levels compared with the negative control ($p < 0.05$), showing comparable effects to Simvastatin. The 50 mg/kg BW dose did not significantly reduce total and LDL cholesterol but produced the highest HDL level. All treatment groups showed a significantly lower Atherogenic Index of Plasma (AIP) than the negative control, with the lowest AIP in the 50 mg/kg BW group. These findings demonstrate the cardioprotective potential of red ginger extracted with NADES as a natural, environmentally friendly approach to preventing dyslipidemia and atherosclerosis.

Kata kunci:

Aterosklerosis
Dislipidemia
Profil lipid
Natural Deep Eutectic Solvent
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ABSTRAK

Aterosklerosis, sebagai penyebab utama penyakit kardiovaskular, berkaitan erat dengan dislipidemia. Penelitian ini mengevaluasi efek kardioprotektif jahe merah (*Zingiber officinale* var. *rubrum*) yang diekstraksi menggunakan Natural Deep Eutectic Solvent (NADES) terhadap profil lipid dan risiko aterosklerosis pada tikus yang diinduksi dengan diet aterogenik dan lipopolisakarida (LPS). Tiga puluh ekor tikus jantan Sprague-Dawley dibagi menjadi lima kelompok: kontrol normal, kontrol negatif, kontrol positif (Simvastatin), serta dua kelompok perlakuan yang menerima ekstrak jahe merah dengan dosis 25 mg/kg dan 50 mg/kg berat badan (BB). Setelah 24 hari perlakuan, dosis 25 mg/kg BB secara signifikan menurunkan kolesterol total dan LDL serta meningkatkan HDL dibandingkan kontrol negatif ($p < 0,05$), dengan efek sebanding dengan Simvastatin. Dosis 50 mg/kg BB tidak menurunkan kolesterol total dan LDL secara signifikan, namun menghasilkan kadar HDL tertinggi. Seluruh kelompok perlakuan menunjukkan penurunan signifikan pada Indeks Aterogenik Plasma (AIP) dibandingkan kontrol negatif, dengan nilai terendah pada kelompok 50 mg/kg BB. Hasil ini menunjukkan potensi kardioprotektif jahe merah hasil ekstraksi NADES sebagai pendekatan alami dan ramah lingkungan untuk pencegahan dislipidemia dan aterosklerosis.

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1. INTRODUCTION

Atherosclerosis is a chronic, progressive disorder characterized by the narrowing of arteries due to the accumulation of lipid-rich plaques. It is the underlying pathology of a broad range of cardiovascular atherosclerotic diseases (CVADs) (PERKI, 2022). These include coronary heart disease, cerebrovascular disease, and peripheral arterial disease, which together remain the leading causes of death and disability worldwide, including in Indonesia (Kemenkes, 2016). If left untreated, atherosclerosis can culminate in myocardial infarction and stroke, which are responsible for approximately 85% of cardiovascular-related mortality. Globally, cardiovascular diseases (CVDs) account for about 31% of all deaths, with the prevalence expected to rise further in the coming years, underscoring the urgency of effective preventive and therapeutic strategies (WHO, 2021).

One of the primary risk factors driving atherosclerosis is dyslipidemia, defined by elevated levels of low-density lipoprotein (LDL) cholesterol and triglycerides along with decreased high-density lipoprotein (HDL) cholesterol (Shahjehan et al., 2024). Excess LDL infiltrates the arterial walls, where it undergoes oxidation and contributes to plaque formation. This process, combined with inflammation, oxidative stress, and endothelial dysfunction, accelerates disease progression (Marchio et al., 2019). Although lifestyle modifications and pharmacological treatments are available and effective, there is still a need to develop targeted therapies capable of specifically addressing dyslipidemia.

Red ginger (*Zingiber officinale* var. *rubrum*) has gained attention for its potential benefits in metabolic health, particularly in modulating lipid profiles. Previous studies have demonstrated significant reductions in total cholesterol, LDL, and triglycerides, alongside increases in HDL (Nirvana et al., 2020). These effects are attributed to active compounds such as 6-gingerol and 6-shogaol. Evidence from in silico and in vitro studies indicates that these compounds act on key molecular targets, including PI3K, PPAR-δ, and LOX-1, thereby exerting anti-atherosclerotic effects (Jasaputra et al., 2025). In addition, 6-gingerol has been shown to regulate multiple targets such as TP53, RELA, BAX, CASP3, and BCL2 within lipid and atherosclerosis-related pathways (Wang et al., 2013), while 6-shogaol protects endothelial cells from oxidized LDL-induced injury by inhibiting LOX-1 signaling (Wakhidatun et al., 2024). Together, these findings position red ginger as a promising natural agent for atherosclerosis prevention.

Nevertheless, the therapeutic efficacy of ginger's bioactive compounds can be compromised by heat sensitivity and limitations of conventional extraction methods (Samota et al., 2024). Natural Deep Eutectic Solvent (NADES) technology has emerged as an environmentally friendly extraction approach that preserves bioactivity and improves yield. Recent work identified betaine: lactic acid (1:2) NADES as the most efficient solvent system, producing the highest concentration of gingerol and shogaol at 15.09 mg/g (Yulianita et al., 2024). Despite these encouraging results, comprehensive in vivo evaluation remains necessary to establish the cardioprotective potential of red ginger extracted using NADES, particularly in relation to lipid regulation and cardiovascular health.

2. METHODS

2.1. Tools and Materials

The study employed an analytical balance (LabPro, Indonesia), a Branson 2800 sonicator (USA), a Cole Parmer centrifuge (USA), an Azure Ao Absorbance microplate reader (USA), and Eppendorf Research Plus micropipettes (Germany). Plant material consisted of red ginger (*Zingiber officinale* var. *rubrum*) obtained from PT Papala Muda Perkasa. Additional reagents included Dragendorff's, Liebermann-Burchard, Bouchardat, Mg, HCl, 10% NaOH, glacial acetic acid, $FeCl_3$, standard BR-12 feed, simvastatin (Hexapharm Jaya), CMC-Na, cholesterol (Qin Health Industry, China), goat fat, cholic acid (Tokyo Chemical Industry, Japan), lipopolysaccharide (LPS) O111:B4 from *Escherichia coli*(Sigma Aldrich), HTAB, KH_2PO_4, K_2HPO_4, o-dianisidine, phosphoric acid, Tween 20, ethanol (96%), and the Glory Reagent kit for lipid profile analysis. Male Sprague-Dawley rats weighing 150–200 g were also used.

2.2. Plant Material

Red ginger was sourced from PT Papala Muda Perkasa, Depok City, West Java, Indonesia, and identified as *Zingiber officinale* var. *rubrum* (family Zingiberaceae) with the identification number 996/IPH.11.02/If.1.1/I/2023.

2.3. Extraction of Red Ginger

Extraction followed the procedure of Yulianita et al. (2024). Red ginger powder was subjected to ultrasound-assisted extraction using NADES (betaine:lactic acid, 1:2) and, for comparison, 96% ethanol. One gram of powder was combined with 10 mL of solvent and sonicated at 50 °C for 30 minutes. The extract was centrifuged at 2700 rpm for 25 minutes, and the supernatant was collected for further analysis.

2.4. Phytochemical Screening

Qualitative analysis of red ginger powder and extract was conducted using colorimetric reactions: Dragendorff's reagent for alkaloids, ferric chloride for phenolics and tannins, and Liebermann-Burchard reagent for triterpenoids and steroids. The tests were performed following Harborne (2015), providing a preliminary profile of secondary metabolites.

2.5. Ethical Approval

All experimental procedures were approved by the Animal Ethics Committee of the Faculty of Mathematics and Natural Sciences, Pakuan University, Bogor, Indonesia (Approval No. 005/KEPHP-UNPAK/02-2024).

2.6. Animal Preparation

Thirty male Sprague-Dawley rats, five months old and weighing 193 ± 20.10 g, were used. Animals were housed under controlled conditions with a 12:12-hour light-dark cycle, humidity of 73%–79%, and temperature of 25 ± 2 °C. After a seven-day acclimatization period, rats were provided free access to standard chow and water.

2.7. *In vivo* Cardioprotective Evaluation

After acclimatization, all groups except the normal control received an atherogenic diet consisting of 2% cholesterol, 5% goat fat, and 0.2% cholic acid, supplemented with standard feed to 100%, administered at 20 g/day in pellet form. During the final week, LPS (0.05 mg/0.1 mL) was administered intranasally three times to exacerbate the model. Rats were divided into five groups:

1. Normal control: standard feed only.
2. Negative control: atherogenic diet + LPS.
3. Positive control: atherogenic diet + Simvastatin (0.18 mg/kg BW) + LPS.
4. Treatment 1 (EJM1): atherogenic diet + red ginger extract (25 mg/kg BW) + LPS.
5. Treatment 2 (EJM2): atherogenic diet + red ginger extract (50 mg/kg BW) + LPS.

2.8. Lipid Profile Measurement and Atherogenic Index Calculation

Serum total cholesterol, HDL cholesterol, and triglycerides were analyzed using the Glory Reagent kit, following the manufacturer's protocol. Absorbance was measured at 500 nm. LDL cholesterol was calculated using the Friedewald equation (Friedewald et al., 1972):

$$LDL - C = TC - HDL\text{-}C - \frac{TG}{5}$$

Percentage change in lipid parameters was calculated as:

$$Percentage\ change\ (\%) = \frac{(Final\ value\ -\ Initial\ value)}{Initial\ value} \times 100\%$$

The Atherogenic Index of Plasma (AIP) was calculated using the formula (Niroumand et al., 2015):

$$AIP\ = \frac{(Total\ cholesterol\ -\ HDL\ cholesterol)}{HDL\ cholesterol}$$

Higher AIP values indicate greater cardiovascular risk.

2.9. Statistical Analysis

Data were analyzed using SPSS version 29. The Kolmogorov–Smirnov test was used to assess normality. One-way ANOVA followed by Duncan's multiple range test was applied to evaluate group differences, with statistical significance set at $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1. Characterization of Red Ginger Simplicia and Extract

Organoleptic evaluation of red ginger powder showed a distinct spicy taste, characteristic aroma, and yellowish-brown color. The moisture content was 9.6%, fulfilling the Indonesian Herbal Pharmacopeia requirement of less than 10%. The ash content was 4.59%, also within the permissible limit of less than 5.6%. The extract obtained was a brown liquid with a total yield of gingerol and shogaol up to 15.09 mg/g (Yulianita et al., 2024). This indicates that the NADES extraction method was effective in isolating active compounds.

3.2. Phytochemical Screening of Simplicia and Extract

Phytochemical analysis revealed the presence of alkaloids, flavonoids, phenolics, glycosides, saponins, and triterpenoids/steroids in both the powder and extract. These secondary metabolites are known to play significant roles in lipid metabolism and cardioprotection.

3.3. Effects of Red Ginger Extract on Lipid Profiles and Atherosclerosis Risk

The cardioprotective effects of NADES-extracted red ginger were evaluated by examining changes in serum lipid profiles and the Atherogenic Index of Plasma (AIP) in rats induced with an atherogenic diet and LPS. **Tables 1 to 3** summarize the effects of red ginger extract compared to controls.

After 24 days, total cholesterol levels (**Table 1**) were significantly reduced in the simvastatin and EJM1 (25 mg/kg BW) groups compared with the negative control ($p < 0.05$). LDL cholesterol showed a similar trend, with marked reductions in both simvastatin and EJM1 groups. In contrast, EJM2 (50 mg/kg BW) did not significantly decrease total or LDL cholesterol compared with the negative control ($p > 0.05$). HDL cholesterol levels were significantly higher in all treatment groups relative to the negative control ($p < 0.05$). The highest HDL values were observed in the EJM2 group, suggesting that this dose is most effective in enhancing HDL levels. Triglyceride levels did not show significant differences among groups, though a downward trend was noted, particularly in the simvastatin group.

Table 1. Lipid profile in experimental animals on day 24

Groups	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Negative Control	202.80 ± 6.14c	109.64 ± 5.31a	17.00 ± 3.43a	148.31 ± 31.10c
Positive Control (Simvastatin)	138.52 ± 21.30a	98.07 ± 17.20a	35.47 ± 11.57b	40.57 ± 27.41a
EJM1	166.47 ± 4.31ab	111.30 ± 23.29a	61.23 ± 18.50b	68.88 ± 28.61ab
EJM2	184.83 ± 28.09bc	106.06 ± 11.72a	69.30 ± 17.51b	121.07 ± 35.22bc

Note: EJM = red ginger extract. Values with different superscripts within a column indicate significant differences ($p < 0.05$).

The percentage change analysis (**Table 2**) further supported these findings. Both simvastatin and EJM1 markedly reduced total cholesterol and LDL compared with the negative control. Although EJM2 showed less reduction, it still demonstrated improvements relative to untreated animals. Triglyceride levels showed a non-significant downward trend in treated groups. HDL values increased across all treatments, with EJM1 and simvastatin producing more stable improvements.

The AIP values (**Table 3**) confirmed these trends. The negative control group exhibited the highest AIP (0.708 ± 0.09), indicating a high cardiovascular risk. Simvastatin and EJM1 reduced the AIP to moderate levels (0.233), while EJM2 achieved the lowest AIP (0.182 ± 0.06).

Table 2. Percentage change in lipid profile

Groups	Total Cholesterol (%)	Triglycerides (%)	HDL (%)	LDL (%)
Negative Control	+10.43 ± 3.46c	+20.61 ± 4.56c	-8.02 ± 0.03a	+15.17 ± 0.05c
Positive Control (Simvastatin)	-11.48 ± 1.12a	-11.22 ± 1.89a	+3.61 ± 0.01c	-25.06 ± 0.28b
EJM1	-7.55 ± 1.10b	-7.55 ± 1.82ab	+2.30 ± 0.01bc	-11.24 ± 0.09bc
EJM2	-6.55 ± 1.92b	-6.55 ± 1.05b	+1.60 ± 0.004b	-5.37 ± 0.03c

Note: (–) indicates a decrease; (+) indicates an increase in lipid levels.

Table 3. Average Atherogenic Index of Plasma (AIP) in all groups

Groups	AIP	Atherosclerosis Risk Status
Negative Control	0.708 ± 0.09	High
Positive Control (Simvastatin)	0.233 ± 0.06	Moderate
EJM1	0.233 ± 0.13	Moderate
EJM2	0.182 ± 0.06	Moderate

Note: AIP risk categories – Low: 0.3–<0.1; Moderate: 0.1–<0.24; High: ≥0.24.

The use of NADES in red ginger extraction preserved thermolabile bioactive compounds, as reported previously (Craveiro et al., 2016; Hsieh et al., 2020). The high yield of gingerol and shogaol obtained with betaine:lactic acid NADES (Yulianita et al., 2024) likely contributed to the improvements observed in lipid profiles and AIP. The reduction in total and LDL cholesterol, combined with elevated HDL levels, underscores the hypolipidemic and cardioprotective potential of red ginger. These results are consistent with earlier studies reporting lipid-lowering effects of red ginger extracts (Mahmudati, 2016; Boroujeni et al., 2016). Interestingly, the 25 mg/kg BW dose (EJM1) was more effective than the 50 mg/kg BW dose (EJM2) for total and LDL cholesterol reduction. This may indicate a biphasic dose-response, a phenomenon where lower doses stimulate beneficial metabolic pathways more effectively than higher doses, which can lead to receptor desensitization or metabolic saturation (Jodynis-Liebert & Kujawska, 2020).

The elevated HDL cholesterol in the EJM2 group highlights the possibility that higher doses are particularly effective in promoting reverse cholesterol transport. However, since HDL alone is not sufficient to counterbalance elevated LDL, the overall lipid profile improvement was more consistent at the lower dose. The observed effects may also be explained by the antioxidant and anti-inflammatory activities of gingerol and shogaol. These compounds have been reported to activate PPAR-α receptors and inhibit HMG-CoA reductase, modulating lipid metabolism (Chen et al., 2018; McCann & Ratneswaran, 2019). The addition of LPS in this model induced systemic inflammation, a known factor that exacerbates atherosclerosis (Gorabi et al., 2022). The improved lipid profiles and reduced AIP in red ginger-treated groups likely reflect both lipid-regulating and anti-inflammatory actions.

Although triglyceride reductions were not statistically significant, percentage change analysis indicated notable decreases compared with the negative control, suggesting that longer treatment durations may produce more pronounced effects. The reduction in AIP across all treatment groups confirms the cardioprotective potential of red ginger. These results align with Shaito et al. (2020), who emphasized the ability of medicinal plants to reduce atherosclerosis risk through lipid modulation, antioxidant activity, and anti-inflammatory mechanisms.

Limitations of this study include the short duration (24 days) and the absence of histopathological analysis to confirm plaque reduction. Future studies should extend treatment duration, incorporate inflammatory and oxidative stress biomarkers (e.g., IL-6, TNF-α, CRP), and perform tissue analyses to validate the cardioprotective effects of NADES-extracted red ginger. Overall, these findings support the potential of red ginger extract as a natural therapeutic for dyslipidemia and atherosclerosis, with NADES technology offering a sustainable method to maximize its bioactivity.

4. CONCLUSION

This study demonstrated that red ginger (*Zingiber officinale* var. *rubrum*) extracted using Natural Deep Eutectic

Solvent (NADES) exhibits significant cardioprotective effects in a rat model of atherosclerosis. Administration of 25 mg/kg BW extract effectively reduced total cholesterol and LDL while elevating HDL, showing efficacy comparable to simvastatin. The 50 mg/kg BW dose yielded the highest HDL and lowest AIP values, indicating further potential in modulating lipid risk factors. These findings highlight red ginger as a promising natural intervention for dyslipidemia and atherosclerosis, while also emphasizing the utility of NADES as a green extraction technology. Longer-term studies and clinical validation are recommended to confirm its therapeutic application.

AUTHOR CONTRIBUTIONS

Conceptualization, Yulianita and Nina Herlina; methodology, Yulianita, Nina Herlina, and Marybet Tri Retno Handayani, with contributions from Novandi Masis Al Aziz, Aditia Safitri, and Ragil Raihan Pamungkas; validation, Yulianita, Nina Herlina, and Marybet Tri Retno Handayani; formal analysis (SPSS), Novandi Masis Al Aziz, Aditia Safitri, and Ragil Raihan Pamungkas; investigation, Novandi Masis Al Aziz, Aditia Safitri, and Ragil Raihan Pamungkas; resources, Novandi Masis Al Aziz, Aditia Safitri, and Ragil Raihan Pamungkas; data curation, Yulianita and Marybet Tri Retno Handayani; writing—original draft preparation, Novandi Masis Al Aziz and Aditia Safitri; writing—review and editing, Nina Herlina, Yulianita, and Marybet Tri Retno Handayani; visualization, Novandi Masis Al Aziz and Ragil Raihan Pamungkas; supervision, Nina Herlina (Principal Investigator of the grant) and Yulianita (main academic supervisor); project administration, Nina Herlina; funding acquisition, Nina Herlina.

All authors have read and agreed to the published version of the manuscript. The corresponding author is Nina Herlina.

INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Animal Ethics Committee of the Faculty of Mathematics and Natural Sciences, Pakuan University, Bogor, Indonesia (Approval No. 005/KEPHP-UNPAK/02-2024).

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

The data supporting this study are available on reasonable request from the corresponding author.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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