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RESEARCH ARTICLE

Antidyslipidaemic effect of *Ipomoea batatas* L. extract with increased PCSK-9 levels in atherosclerotic rats

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Abstract

Atherosclerosis is the largest cause of mortality worldwide, and Low-Density Lipoprotein (LDL) is a primary risk factor for this illness. The purpose of this research was to determine the effect of purple sweet potato (*Ipomoea batatas* L.) extract on cholesterol, LDL, PCSK9, and MDA levels in rats fed a high-cholesterol diet. This true experimental study used a randomized pre-test-post-test control group design. Wistar rats were randomly assigned to three groups. Purple sweet potato extract (PSPE) was prepared by 24-hour maceration with 70% ethanol. All rats were fed a high-cholesterol diet for 14 days, followed by pre-test measurements of cholesterol, LDL, PCSK9, and MDA on day 15. Rats were then randomly divided into control (no treatment), PSPE (200 mg/day), and Simvastatin (0.9 mg/kg BW) groups. After one month of treatment, post-test analyses were performed for all parameters. The results showed an increase in serum cholesterol, LDL and MDA levels in rats fed a high-cholesterol diet ($p<0.05$) compared to the PSPE and Simvastatin groups. The high-cholesterol diet also resulted in a significant ($p<0.05$) decrease in PCSK9 when compared to the PSPE and Simvastatin groups. In the PSPE group there was a decrease in cholesterol, LDL, and MDA, and PSPE ($p<0.05$) compared to the control group. In the Simvastatin group, the increase in PCSK9 was very low compared to the PSPE group. PSPE has antidyslipidaemic activity by reducing total cholesterol status, LDL, and oxidative stress while promoting PCSK-9 function. Further research is required to provide a comprehensive understanding of the mechanism of action of PSPE as an antioxidant source in patients with atherosclerosis.

1. INTRODUCTION

Dyslipidaemia is perceived as a critical risk factor for atherosclerotic cardiovascular disease (ASCVD), which includes ischemic stroke (IS), coronary artery disease (CAD), and peripheral arterial disease (PAD) (1,2). Several European and American medical association recommendations have advised the use of high-intensity statins (HIS) in high-risk patients to decrease low-density lipoprotein cholesterol (LDL-C) and reduce the risk of ASCVD (3). In high-risk individuals who have never even reached their LDL-C targets at a tolerable statin dosage, the inhibitor ezetimibe and the proprotein convertase subtilisin/Kexin type-9 (PCSK9) should be used in association with statin therapy (4). PCSK9 inhibitors target PCSK9, reducing the amount of LDL receptor degradation in hepatocytes. This increases LDL clearance and lowers blood levels of LDL-C (5,6). Studies using experimental animals have shown that PCSK9 may degrade additional receptors in addition to LDL-C, such as CD36, which suggests its role in endothelium, inflammation, and homeostasis (7).

Two forms of PCSK9 inhibitors, alirocumab and evolocumab, have been clinically indicated and proven to reduce the risk of ASCVD. Statins, particularly simvastatin, are known to have a limited impact since they may lower plasma LDL-

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C but also trigger Sterol Regulatory Element-Binding Protein-2 (SREBP2) translocation, which increases PCSK9 gene expression (8). Similarly, the usage of alirocumab and evolocumab has shown an association between decreased LDL-C levels and decreased cardiovascular risk, particularly in adults with atherosclerotic cardiovascular disease (9,10). In an effort to inhibit PCSK9 activity, monoclonal antibodies and antisense oligonucleotides are also very effective in lowering LDL receptor degradation and enhancing LDL-C clearance (11-15). However, the drug price is still rather high, and its adverse effects impede its use; moreover, its treatment is long-term. The implementation of biological techniques derived from natural substances or extracts that are deemed optimum for inhibiting PCSK-9 requires intensive study at present.

Several plant-derived dietary peptides consumed regularly may reduce LDL-C by a mechanism similar to that of statins (16). Studies have revealed that berberine fruit extract acts as a lipid-lowering agent by inducing low-density lipoprotein receptor (LDLR) expression and inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase (14,15). Surprisingly, a similar mechanism was established in flaxseed peptides (*Cannabis sativa* L.) (*Cannabaceae*), which exhibited hypocholesterolaemic action (17). In vitro, anthocyanins from mulberries inhibited the expression of SREBP2, resulting in a consistent reduction in PCSK-9 expression. Our previous research combining simvastatin with purple sweet potato *(Ipomoea batatas* L.) extract capsules reduced cholesterol and LDL levels more effectively than simvastatin alone in dyslipidaemic individuals. Therefore, this study aims to confirm the molecular mechanism (PCSK9) in an animal model (18). Purple sweet potato extract (PSPE) is rich in flavonoid metabolites and has been demonstrated to modulate fatty acid synthase as part of the mechanism of action to enhance the profile of mice (FAS) (19,20). Flavonoids may influence the transcription factor SREBP-2, which plays a role in enhancing LDL receptor expression and decreasing PCSK9 expression at the molecular level. This study aimed to evaluate the effect of purple sweet potato extract on PCSK9 expression and lipid profiles in hypercholesterolaemic rats.

Therefore, we hypothesized that supplementation with PSPE would lower serum cholesterol and LDL levels, downregulate PCSK9 expression, and reduce MDA levels in rats subjected to a high-cholesterol diet, indicating both lipid-lowering and antioxidant effects. We also hypothesize that, in addition to providing significant effects on these parameters, administration of PSPE will also provide a mechanistic basis for its potential as a functional food in managing hypercholesterolaemia and oxidative stress.

2. MATERIALS AND METHODS

2.1. Ethical Clearance

This study's ethical clearance statement has been approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University (UNUD), Bali Province, Indonesia with Protocol No. 2022.03.1.0636.

2.2. Research Design

This research is part of an experimental laboratory investigation using a randomized pre-and post-test design. In this study, 27 male Wistar rats meeting the inclusion criteria of 2 to 3 months of age, 200 to 225 grams of body weight, and good health were used as test subjects. The sample size was calculated based on Federer's equation. To compensate for potential attrition (e.g., mortality or morbidity during the study), a 10% buffer was added to the total sample, resulting in a total sample size of 30 rats. Male rats were acclimatized for two weeks and fed *ad libitum* with a commercial diet. On the fifteenth day, pre-test lipid profile measurements of total cholesterol, LDL levels, PCSK9, and MDA were conducted, followed by random assignment. The Wistar rats were then divided into three groups of nine rats each: 1) the control group (high-cholesterol diet); 2) the PSPE group (high-cholesterol diet + PSPE 200 mg/day/rat); and 3) the simvastatin group (high-cholesterol diet + 0.9 mg/kg BW).

2.3. Preparation of PSPE

Farmers in Tabanan Regency, Bali Province, obtained fresh purple sweet potatoes of medium size and brownish-purple hue from their farms. Fresh purple sweet potatoes were washed thoroughly under running clean water. The purple sweet potato was then sliced into small uniform pieces and dried in a 50°C oven for 24 hours to produce dry simplicia suitable for extraction in the subsequent step. A total of 100 g of purple sweet potato simplicia was extracted using 70% ethanol containing 3% (w/v) citric acid at a ratio of 1:10 (w/v). Maceration was carried out for 24 hours at room temperature. Citric acid was added to stabilize anthocyanin compounds and inhibit oxidation during the extraction process. The extract was then concentrated using a rotary vacuum evaporator at 40°C and a pressure of 70-80 mbar to yield a thick concentrated extract. The extraction yield of purple sweet potato extract (PSPE) was 15 g from 100 g of simplicia. The resulting PSPE was subsequently reconstituted to a working concentration of 200 mg/mL (18,19,21).

2.4. Treatment

The rats were fed routinely throughout the acclimatization period, with the nutritional content of the diet consisting of protein (20-25%), fat (5%), carbohydrates (45-50%), crude fiber (5%), ash (4%), vitamins and minerals. The total fat content of the feed increased to 13.6% following the addition of 10% lard. On day 15, prior to the high-cholesterol diet

intervention, pre-test data were collected, including body weight, total cholesterol levels, LDL cholesterol, PCSK9 levels, and blood MDA. Subsequently, 27 male Wistar rats were randomly allocated into three groups of nine rats each. The high-cholesterol diet used in this study was obtained from the Nutrition Laboratory, Centre for Food Studies, Gadjah Mada University, Yogyakarta, and comprised the following composition: water (12%), crude protein (19%), crude fat (4%), ash content (6.5%), calcium (1.1%), phosphorus (0.9%), and supplemental lard (10%). For a month, the high-cholesterol diet was provided *ad libitum* according to the following group specifications:

- **Hypercholesterolemic Control Group**: rats received a high-cholesterol diet only;
- **PSPE Group**: rats received a high-cholesterol diet supplemented with PSPE at 200 mg/day;
- **Simvastatin Group**: rats received a high-cholesterol diet supplemented with simvastatin at 40 mg/kg body weight

Total cholesterol, LDL, PCSK9, and MDA levels were measured in each group following a one-month intervention period to obtain post-test results. Blood samples for pre- and post-test measurements were collected from the retro-orbital sinus of each rat (21).

2.5. Determination of Total Cholesterol Levels

Total cholesterol levels were determined using the Cholesterol FS Kit (DiaSys, USA; Cat No. 1 1300 99 10 030). Briefly, 10 µL of Wistar rat serum and 10 µL of calibrator standard were pipetted into separate labelled tubes. An additional 10 µL of distillate water was prepared as a reagent blank. To each tube, 1,000 µL of working reagent was added and mixed thoroughly, then incubated for 10 minutes at 20–25°C. Absorbance was measured using UV-Vis spectrophotometry at a wavelength of 500 nm for 60 minutes against the reagent blank. Total cholesterol concentration was calculated according to Equation 1.

$$Cholesterol\ (mg/dL) = \frac{A.Sample}{A.Std/Cal} \times Cons.Std/Cal\ (mg/dL) \quad (1)$$

2.6. Low-Density Lipoprotein (LDL)

Low-density lipoprotein (LDL) cholesterol levels were measured using the LDL Precipitant Kit (DiaSys, USA; Cat No. 1: 4330 99 90 885). The 100 µL serum sample was mixed with 1,000 µL of precipitating reagent, gently vortexed and incubated for 15 minutes at room temperature. The mixture was then centrifuged at 2,500 g for 20 minutes. Within one hour of centrifugation, 100 µL of the resulting clear supernatant was transferred to the reaction solution for LDL cholesterol quantification. Absorbance was measured within 45 minutes against a reagent blank. LDL cholesterol concentration was calculated according to Equation 2.

$$LDL\ Cholesterol\ (mg/dL) = Total\ Cholesterol - Cholesterol\ in\ The\ Supernatant \quad (2)$$

2.7. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Assay

Serum proprotein convertase subtilisin/Kexin type 9 (PCSK9) levels were quantified using the Rat PCSK9 ELISA Kit (MyBioSource, USA; Cat No: MBS2515956). Briefly, 100 µL of standard or sample was added to each well and incubated at 37°C for 90 minutes. The liquid was then aspirated, and 100 µL of Biotinylated Antibody Detection (Ab) was added to each well, followed by incubation at 37°C for 60 minutes. Wells were aspirated and washed three times. Subsequently, 100 µL of HRP-conjugated was added and incubated at 37°C for 30 minutes, followed by aspirated once and five washes. Next, 90 µL of reagent substrate solution was added and incubated at 37°C for 15 minutes. Finally, 50 µL of stop solution was added to each well and absorbance was measures at 450 nm using a microplate reader.

2.8. Malondialdehyde (MDA)

Serum malondialdehyde (MDA) levels were quantified using the Rat Malondialdehyde ELISA Kit (My Biosource, USA; Cat No: MBS268427). Briefly, all reagents, samples, and standards were prepared according to the manufacturer's instructions and equilibrated to room temperature prior to use. Standards and prepared samples were added to the appropriate wells and incubated at 37°C for 90 minutes. Wells were washed twice and Biotinylated Antibody working solution was added and incubated at 37°C for 60 minutes. After three washes, enzyme-conjugate working solution was added and incubated at 37°C for 30 minutes. Following five washes, 100 µL of color reagent solution was added to each well, including blank wells and incubated at 37°C in the dark until a visible color gradient developed among the standards, not exceeding 30 minutes. The reaction was terminated by adding 100 µL of color reagent C to each well. The plate was mixed gently and absorbance was measured at 450 nm using a microplate reader within 10 minutes.

2.9. Statistical Analysis

All data were tabulated using Microsoft Excel 2019 (Microsoft, USA). Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corporation, USA). Data normality was assessed using the Kolmogorov-Smirnov test and homogeneity of variances was evaluated using Levene's test. Paired samples t-test were used to compare pre- and post-

treatment values within group. One-way ANOVA was used to compare means across groups and post-hoc analysis was performed using Duncan's Multiple Range Test (DMRT) at a significance confidence interval of $p<0.05$. Results are presented as figures and tables. All graphical illustrations were generated using GraphPad Prism version 8.0 (GraphPad Software, Inc, USA).

3. RESULTS AND DISCUSSION

3.1. Total Cholesterol Levels

The mean total cholesterol levels at pre-test were 130.36±1.69 mg/dL in the control group, 130.28±0.85 mg/dL in the PSPE group, and 130.36±2.79 mg/dL in the simvastatin group with no statistically significant difference among groups ($p>0.05$). Following one month of a high-cholesterol diet, total cholesterol in the control group increased significantly to 165±1.51 mg/dL ($p<0.05$). In the PSPE 200 mg/day group, total cholesterol decreased significantly from 130±0.85 to 119±1.34 mg/dL ($p<0.05$). Similarly, the simvastatin 40 mg/kg body weight demonstrated a significant reduction from 130.36±2.80 to 112.12±0.96 mg/dL ($p<0.05$) (Figure 1). Notably, the cholesterol-lowering effect of PSPE was not significantly different from that of simvastatin ($p>0.05$), suggesting that PSPE may have antidyslipidaemic capabilities.

3.2. LDL Levels

The mean±SD pre-test LDL values across the three groups were comparable: control (39.50±5.00 mg/dL), PSPE (39.4±1.54 mg/dL), and Simvastatin (39.3±3.84 mg/dL) with no statistically significant differences among groups ($p>0.05$). Administration of a high-cholesterol diet resulted in a marked increase in LDL levels in the control group reaching 60.50±2.04 mg/dL at post-test. In contrast, both treatment groups showed statistically significant reduction in LDL levels at post-test ($p<0.05$), with the PSPE and simvastatin groups achieving values of 27.56±0.55 mg/dL and 16.11±0.82 mg/dL, respectively. These findings indicate that PSPE was effective in reducing LDL levels in hypercholesterolemic rats. However, LDL levels in the PSPE group remained significantly higher than those in the simvastatin group (Figure 2).

Proprotein convertase subtilisin/Kexin type 9 (PCSK9) is a serine protease enzyme/protein predominantly synthesized by the liver that regulates plasma LDL cholesterol levels by modulating the expression and recycling of LDL receptors (LDLR) on hepatocytes surfaces (22). PCSK9 regulates LDLR abundance through a post-translational mechanism by binding to the extracellular domain of LDLR and directing it toward lysosomal degradation, thereby reducing receptor availability for LDL clearance (23,24). As a result, PCSK9 represents an established therapeutic target for lowering circulating LDL levels. Pharmacological inhibition of PCSK9 has been demonstrated as an effective adjunct therapy for LDL reduction (25).

Elevated circulating PCSK9 levels promote the degradation of LDLR and elevated plasma LDL (24). Conversely, reduced PCSK9 levels allow LDLR to be recycled to the hepatocyte surface, thereby enhancing LDL clearance from circulation and lowering plasma LDL (26). Several nutraceuticals have been reported to modulate PCSK9 expression through diverse molecular pathways, contributing to LDL reduction (27). The mechanism underlying LDL reduction via PCSK9 modulation centers on PCSK9-mediated regulation of hepatic LDLR turnover. By promoting lysosomal degradation of LDLR, PCSK9 limits receptor availability and elevates plasma LDL-C. Pharmacological PCSK9 inhibition, as achieved with monoclonal antibodies such as evolocumab or alirocumab, abrogates this degradation pathway, resulting in upregulated hepatic LDLR expression and enhanced systemic LDL-C clearance. Among nutraceutical compounds, quercetin has been shown to downregulate PCSK9 protein expression, thereby preserving LDLR on the hepatocyte surface and facilitating greater LDL cholesterol uptake from circulation, ultimately leading to a significant reduction in plasma LDL-C levels (26).

3.3. PCSK-9 Levels

Analysis of PCSK9 levels across treatment groups at the pre-test phase revealed no significant differences ($p > 0.05$). At the post-test phase, PCSK9 levels in the hypercholesterolemic control group increased significantly to 162.24±1.5 ng/mL ($p < 0.05$) compared to those in the PSPE and simvastatin groups (Figure 3). PCSK9 levels in the PSPE group remained significantly higher (66.39±1.0 ng/mL) than those in the simvastatin group (11.66±0.3 ng/mL) at the post-test stage. These findings suggest that bioactive compounds present in PSPE may contribute to the maintenance of PCSK9 levels within a lower range even under hypercholesterolemic conditions induced by a high-cholesterol diet. Nevertheless, long-term studies are required to confirm the sustained regulatory effects of PSPE-derived compounds on PCSK9 expression, which could position PSPE as a safe alternative therapeutic agent for individuals with hypercholesterolemia.

The secondary metabolites present in PSPE are capable of stimulating LDLR expression through mechanisms comparable to the inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase by statin-class drugs, as previously demonstrated in studies examining the efficacy of berberine extract (28). In vitro experiments have demonstrated that incubating quercetin in its glycosylated form with HepG2 cells at concentrations ranging from 1 to 10 µM reduced PCSK9 mRNA levels by 20-30%. In addition to hepatocytes, quercetin was also found to inhibit PCSK9 expression in macrophage cell populations in the present investigation (29). The findings of the present study further

confirmed PSPE's anti-atherogenic activity, evidence by direct reductions in total cholesterol, LDL, and PCSK9 levels, all of which are closely associated with lipid metabolism. Consistent with prior literature, quercetin has demonstrated both direct anti-atherogenic effects and LDL-cholesterol-independent mechanisms that may limit cholesterol absorption in the body (30).

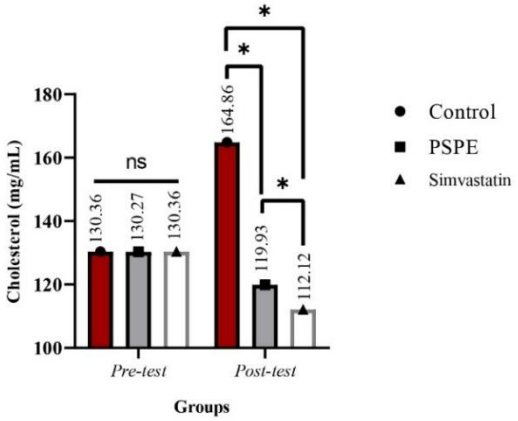

Figure 1. Total cholesterol levels of hypercholesterolemic Wistar rats (n = 9). Based on the paired T-test (pre-test and post-test) and an independent test between groups, the * sign indicates a significant difference (P < 0.05), whereas NS indicates no significant difference (P > 0.05)

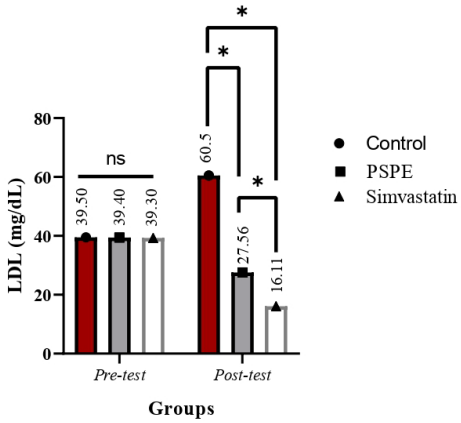

Figure 2. LDL levels of hypercholesterolemic Wistar rats (n = 9). Based on the paired T-test (pre- and post-test) and an independent test between groups, the * sign indicates a significant difference (P < 0.05), whereas NS indicates no significant difference (P > 0.05)

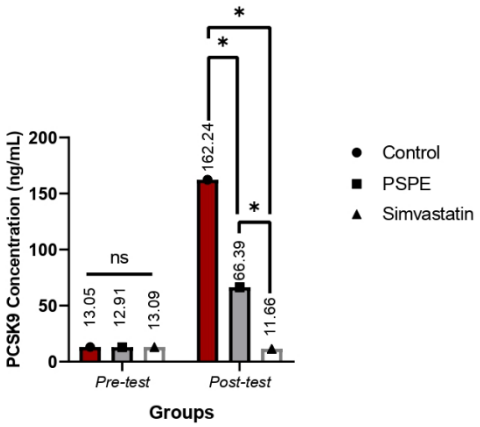

Figure 3. PCSK9 levels of hypercholesterolemic Wistar rats (n=9). Based on the paired T-test (pre-and post-test) and an independent test between groups, the * sign indicates a significant difference (P <0.05), whereas NS indicates no significant difference (P > 0.05)

3.4. Malondialdehyde (MDA) Levels

At the pre-test stage, oxidative stress as assessed by malondialdehyde (MDA) levels revealed no significant differences between treatment groups (Figure 4). At the post-test measurement, MDA levels in the control group reached the highest value in this study at 3.25±0.10 mmoL/mL. In comparison, MDA levels in the PSPE and simvastatin groups at the same time point were 1.11±0.05 mmoL/mL and 0.87±0.061 mmoL/mL, respectively. These findings suggest that the antioxidant properties of PSPE may attenuate the development of oxidative stress in male rats fed a high-cholesterol diet.

PSPE treatment in the present study also demonstrated significance in reducing free radical generation, as reflected by lower MDA levels. Flavonoids present in natural plant-derived compounds have been shown in multiple studies to protect against increase in free radical production, including in obese women (31) and in hyperuricemia rats models, where they also reduced TNF-α and other oxidative stress markers (32).

Flavonoids exert antioxidant effects at both intracellular and extracellular levels (18,19,21). One critical mechanism involves the inhibition of xanthine oxidase (XO), which under ischemia-reperfusion conditions convert to xanthine dehydrogenase (XD), thereby attenuating free radical generation (33,34). Flavonoids in natural agents are also reported to inhibit pro-oxidant enzymes such as nitric acid synthase (35), lipoxygenase, and cyclooxygenase, and to suppress lipopolysaccharide-induce expression of inducible nitric oxide synthase (iNOS) genes (36,37), thereby mitigating oxidative damage.

Quercetin, a flavonoid compound, has been shown to reduce LDL levels in hypercholesterolemic Wistar rats through modulation of cholesterol metabolism and improvement of lipid profiles. This effect is achieved primarily through inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), a key enzyme in the cholesterol biosynthesis pathway, thereby reducing endogenous cholesterol production (38).

Flavonoids exert their PCSK9-lowering effects primarily at the transcriptional level suppressing PCSK9 mRNA expression, which subsequently reduces PCSK9 protein synthesis and increases LDL receptor (LDLR) availability on hepatocyte surfaces. Specific flavonoid compounds, including 3,7,2'-trihydroxy-5-methoxy-flavanone and skullcap flavone II, have been shown to suppress PCSK9 expression through modulation of the sterol regulatory element-binding protein 1 (SREBP-1) signaling pathway, leading to upregulation of LDLR protein levels and enhanced clearance of LDL from the circulation (39).

Flavonoid glycosides from *Epimedium koreanum* similarly suppress PCSK9 mRNA expression and upregulate LDLR, indicating improved LDL uptake (40). Mechanistic studies further suggest that certain flavonoids act via allosteric inhibition of PCSK9 or direct binding to its catalytic domain, reducing PCSK9 activity and preventing LDLR degradation, there by promoting LDLR recycling and lowering circulating LDL cholesterol (41). Collectively, these mechanisms suggest that natural flavonoids, including those present in PSPE, are promising candidates for modulating lipid metabolism through the reduction of PCSK9 levels and activity. However, further investigation is required to confirm these mechanisms and their clinical relevance. Based on the present findings, PSPE demonstrates promising therapeutic potential for the management of hyperlipidaemia.

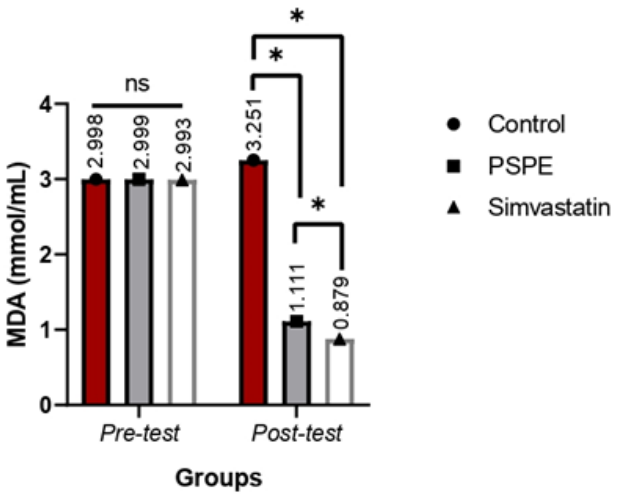

Figure 4. MDA levels in hypercholesterolemic Wistar rats (n=9). Based on the paired T-test (pre- and post-test) and an independent test between groups, the * sign indicates a significant difference (P <0.05), whereas NS indicates no significant difference (P > 0.05).

4. CONCLUSIONS

At a dose of 200 mg/day, PSPE reduced total cholesterol, LDL, MDA, and PCSK9 levels in rats fed a high-cholesterol diet, with efficacy approaching that of simvastatin. Further research is warranted to understand the mechanism by which PSPE contributes to vascular protection, including assessment of atherosclerosis-related gene expression, pro-inflammatory cytokine profiles, and histopathological evaluation of the vascular endothelium in high-cholesterol diet-induced rat models.

Author contributions: IWPSY IMJ: Conceived the study, acquired funding and supervisor. ANM: Carried out the investigation and analyzed the data. IGW, PAW: Conducted the resources, edited the manuscript, and critical reviews of the manuscript before submission to the journal website. All authors read the final version of the article and confirmed its publication.

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Ethics statement: All authors have inspected the ethical issues of plagiarism, misconduct, data fabrication, falsification, double publication or redundancy related to the manuscript. This study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University (UNUD), Bali Province, Indonesia (Protocol No. 2022.03.1.0636).

Conflict of interest: The authors declare no conflicts of interest.

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