



Evaluation of the antiatherogenic potential of purple sweet potato (*Ipomoea batatas* L.) extracts in Wistar rats exposed to a high-cholesterol diet

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ABSTRACT

Dyslipidemia caused by elevated low-density lipoprotein cholesterol (LDL-C) is one of the causes of atherosclerosis. This study aims to determine the purple sweet potato extract (PSPE) as an antiatherogenic agent in rats fed a high-cholesterol diet. In total, 32 adult male Wistar rats were separated into two groups. A randomized pre-and posttest control design was performed. Before treatment, the lipid profile and the levels of malondialdehyde (MDA), superoxide dismutase (SOD), protein Netrin-1, and apolipoprotein-E (Apo-E) were all evaluated. Group 1, the control group, received a high-cholesterol diet (control), while Group 2 received a high-cholesterol diet supplemented with 200 mg/ml PSPE. Group 2 hereafter will be mentioned as the PSPE group. Both groups were treated by respective treatment for 3 months. At the end of the treatment, the evaluation of necessary parameters was carried out with the pretest. Paired *t*-test data was obtained. The results showed that the treatment given to Group 2 (high-cholesterol diet supplemented with PSPE) was able to reduce and maintain total cholesterol levels in the posttest by 131.02 ± 4.3 mg/dl when compared to the control group, which was 261.25 ± 18.74 mg/dl in the posttest. There was a significant decrease ($p < 0.05$) in triglyceride (131.27 ± 1.9 mg/dl), LDL (18.33 ± 4.6 mg/dl), and MDA levels (0.6 ± 0.04 mmol/ml) in the PSPE group compared with the control group in the same parameters. However, there was an increase in the levels of high-density lipoprotein (86.43 ± 1.9 mg/dl), SOD (5.22 ± 0.14 U/ml), Netrin-1 (115 ng/l), and Apo-E (107.52 ng/ml) in the serum of posttest on PSPE group, but not shown in the control group. Following our findings, 200 mg/ml PSPE treatment successfully maintained a lipid profile by reducing oxidative stress and increasing Netrin-1 and Apo-E levels in Wistar rats fed a high-cholesterol diet. These findings indicate that PSPE displays antiatherogenic effects and is possible to be utilized as a new atherosclerosis therapy, whose mechanism of action is described in this study.

INTRODUCTION

Atherosclerosis is a severe public health issue responsible for a relatively high mortality rate, particularly in the coronary arteries. Atherosclerosis is expected to be a significant health burden in the future [1]. Atherosclerosis is mainly caused

by various causes, one of which is dyslipidemia. Dyslipidemia, caused mainly by an increase in low-density lipoprotein (LDL) cholesterol, may lead to endothelial dysfunction [2] and is susceptible to oxidative stress and the formation of oxidized LDL, which promotes atherosclerosis [3].

The levels of high-density lipoprotein (HDL), apoprotein A-I (ApoA-I), and apoprotein E (ApoE) levels have previously been utilized as indicators of inflammation caused by dyslipidemia [4]. Netrin-1, a novel protein utilized as a marker of atherosclerosis, has been discovered [5]. Netrin-1 relates to the laminin protein family, which was shown to be an essential

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protein in neuronal proliferation during embryonic development [6]. Following the recent identification of the Netrin-1 receptor in cells other than the central nervous systems Netrin-1 was shown to be implicated in the pathological process that controls multiple degenerative illnesses, such as atherosclerosis [7]. Netrin-1 prevents cardiovascular disease by inhibiting the inflammation process in patients with atherosclerosis. This inflammation inhibition occurs due to the release of macrophages from the endothelium lesion and the entrance of the monocyte into the lesion [8].

Previous research has shown that Netrin-1 decreased inflammation in various oxidative stress approaches. The low levels of Netrin-1, which is frequently observed in the blood sample of type 2 diabetes patients, impacted inflammation [9]. The low level of plasma Netrin-1 in individuals with atherosclerosis and blood vessel wall inflammation was effectively restored by utilizing the recombinant Netrin-1 [10]. The role of Netrin-1 in blood vessels is to maintain the optimum endothelial function as an anti-inflammatory by preventing the adhesion and migration of monocyte [11].

ApoE is a required encoded protein for lipid metabolism [12]. ApoE acts as a mediator for particular cell surface receptors, including those of the LDL family and heparin sulfate proteoglycans which control lipoprotein clearance from plasma [13]. According to a recent study, ApoE in very-low-density lipoprotein can influence lipoprotein lipase activity and has a role in the etiology of metabolic diseases, such as type II diabetes, metabolic syndrome, and cardiovascular disease [14]. According to gene function studies, the mutation of the ApoE gene causes lipid metabolic problems in the rat's liver [15].

Based on the statement above, it is essential to look for natural remedies that can increase blood levels of Netrin-1 and ApoE while lowering total cholesterol. Purple sweet potato is an economic crop with important value in many countries, including Indonesia [16]. Interestingly, apart from being used as a staple food. Purple sweet potato can also act as a source of bioactive compounds that have attracted much attention for development [17]. Recent reports revealed that more than 135 bioactive compounds have been isolated from this plant and those compounds are able to provide good pharmacological activity. Polysaccharides and flavonoids have been developed as bioactive sources for drug-delivery systems [18]. Based on *in vitro* study, purple sweet potato extract (PSPE) has been widely used as an antitumor in HepG2, LOVO, and MCF-7 cell models [17]. Polyphenols isolated from PSPE could promote intestinal epithelial differentiation by upregulating PGC-1 α and increasing the mitochondrial biogenesis of Caco-2 cells [19]. Likewise, *in vivo* studies showed that PAPER has an antihyperuricemia effect by inhibiting xanthine oxidase [20]. Anthocyanin-rich of PSPE can also promote liver function against damage caused by exposure to CCl₄ [21]. In our previous study conducted on laboratory animals, PSPE at a dose of 200 mg/day/rat has been shown to reduce oxidative stress and inflammation and was not significantly different compared to the simvastatin group (standard control) [22,23].

However, the revealed effect of purple sweet potato status on atherosclerotic rats fed a high-cholesterol diet was

limited. A previous study showed that PSPE could decrease the significantly increased oxidative stress caused by a high-cholesterol diet [23]. This study aims to investigate how PSPE influenced lipid profile protein levels of Netrin-1 and ApoE in rats administered with a high-cholesterol diet by decreasing oxidative causes of atherosclerosis.

MATERIALS AND METHODS

Ethical clearance

The Research Ethics Committee of the Faculty of Medicine, Udayana University, had approved this research protocol with approval No. 2021.03.1.1078, dated 07/12/2021.

Research design

This research was included in an experimental laboratory study with a randomized pre-and post-test design. A total of 32 male Wistar rats were adapted for 2 weeks based on inclusion criteria (aged 4 months, weighing 200–300 g, and in healthy condition). Additionally, for 3 months, 32 rats were separated into two groups (16 rats each), the control group (high cholesterol diet) and the PSPE group (high cholesterol diet + PSPE 200 mg/day/rats).

Preparation of PSPE

PSPE was produced by macerating 1 kg of purple sweet potato flour in 3 l of 70% ethanol and acidifying this with 3% citric acid for 24 hours. The maceration performance was obtained and concentrated using a rotating vacuum evaporator at a temperature of 40°C and a pressure of 70–80 mbar to produce a concentrated extract. The concentration of the extract was determined to be 200 mg/ml [22,24].

Rats models and treatment

During the acclimation phase, rats were fed a regular diet that consisted of protein (20%–25%), fat (5%), carbohydrates (45%–50%), crude fiber (5%), ash (4%), and vitamins and minerals. As pretest data, total cholesterol, lipid profile, Netrin-1, Apo-E, malondialdehyde (MDA), and blood superoxide dismutase (SOD) were measured on day 15. It was then followed by random allocation, in which 32 rats were divided into two groups of 16 rats each/groups. The high-cholesterol diet was made using a combination of lard oil (10%), duck egg yolks (5%), and standard feed [25]. The control group was given a high-cholesterol diet. The PSPE group was given a high-cholesterol diet and 200 mg/day/rats of PSPE. For 3 months, a high-cholesterol diet was administered *ad libitum* orally. Total cholesterol, lipid profile, Netrin-1, Apo-E, MDA, and blood SOD levels were measured again 3 months later as posttest data. Blood samples for testing these parameters were taken through the orbital sinus [25].

Lipid profiles

Determination of total cholesterol levels

Total cholesterol level was determined using the Cholesterol FS Kit (DyaSys, USA) (Cat No. 1 1300 99 10 030). In summary, 10 μ l of Wistar rat serum and a standard

was prepared. Furthermore, as much as 10 μl of distillate water was prepared blank reagent for control. 1,000 μl of the reagent and standard mixtures were prepared, mixed, and incubated for 10 minutes at 20°C–25°C. The absorbance value of the sample was read by UV-Vis spectrophotometry at a wavelength of 500 nm for 60 minutes and compared with the blank reagent. The calculation of total cholesterol levels using the following equation:

$$\text{Cholesterol (mg / dl)} = \frac{A_{\text{sample}}}{A_{\text{Std}}} \text{Conc.} \frac{\text{Std}}{\text{Cal}} \left(\frac{\text{mg}}{\text{dl}} \right)$$

Triglycerides (TG)

Determination of serum TG levels was performed by using TG FS (DyaSys, USA) (Cat. No. 1-5700-99-10-030). In summary, 10 μl of Wistar rat serum and 1 μl of distillate water were prepared. Similarly, blank and standard reagents were prepared, 1,000 μl of each. The mixture of distillate water and reagent was used as a blank. Each blank and sample was mixed and incubated for 10 minutes at 20°C–25°C. The absorbance value of the sample was read by UV-Vis spectrophotometry at a wavelength of 500 nm for 60 minutes and compared with the blank reagent. The calculation of total cholesterol levels using the following equation:

$$\text{TG (mg / dl)} = \frac{A_{\text{sample}}}{A_{\text{Std}}} \text{Conc. Std / Cal (mg / dl)}$$

High-density lipoprotein

Determination of HDL levels was performed by using HDL Precipitant (DiaSys, USA) (Cat No. 1: 3540 99 90 885). The first test procedure was precipitation: namely, as much as 200 μl of sample or standard and 500 μl of precipitation reagent were mixed and incubated for 15 minutes at room temperature, then centrifuged for 20 minutes at 2,500 g. Within 2 hours after centrifugation, 0.1 ml of the clear supernatant was transferred to the reaction solution to determine HDL cholesterol levels. The determination of HDL cholesterol was carried out by preparing 100 μl of sample supernatant and 100 μl of standard, respectively. A total of 1,000 μl of cholesterol reagent was added to the standard and sample, mixed, and incubated for 10 minutes at room temperature. Then the absorbance value of the sample or standard was measured using a UV-Vis spectrophotometer at a wavelength of 500 nm. The results were then compared with the reagent blank value within 45 minutes. The calculations are carried out using the following equation:

$$\text{HDL - Choles} \left(\frac{\text{mg}}{\text{dl}} \right) = \frac{\Delta A_{\text{sample}}}{\Delta A_{\text{Std}}} \text{Conc. Std} \left(\frac{\text{mg}}{\text{dl}} \right)$$

The standard concentration is the total cholesterol concentration in a standard cholesterol solution.

Low-density lipoprotein

Determination of LDL levels was performed by using the LDL Precipitant Kit (DyaSys, USA) (Cat No. 1: 4330 99 90 885). The first test procedure was through precipitation; namely, a 100 μl sample and 1,000 μl of precipitation reagent were prepared, mixed, and incubated for 15 minutes at room temperature, then centrifuged for 20 minutes at 2,500 g. Within 1 hour after centrifugation, 100 μl of the clear supernatant was transferred to the reaction solution to determine LDL cholesterol. The determination of LDL cholesterol was carried out similarly to HDL cholesterol. The results were compared with the reagent blank value within 45 minutes. The calculations are carried out using the following equation:

$$\text{LDL - Choles} \left(\frac{\text{mg}}{\text{dl}} \right) = \text{Total cholesterol} - \text{Cholesterol in the supernatant.}$$

Oxidative stress assay

Malondialdehyde

Rat Malondialdehyde ELISA Kit (Bioassay Tech Laboratory, China) MDA levels (Cat. No. E0156Ra) was used to perform the MDA assay. All of the reagents, samples, and standards were prepared, and then the samples and ELISA reagents were added to each well and incubated at 37°C for 1 hour. The ELISA plate was cleaned five times before adding substrate solutions A and B and incubating for 10 minutes at 37°C. When a stop solution was introduced, the color changed from blue to yellow. The optical density (OD value) of each well was assessed using a microplate reader set to 450 nm for 10 minutes.

Superoxide dismutase

SOD levels were determined using the Rat Super Oxidase Dismutase ELISA Kit (Bioassay Tech Laboratory, China) (Cat. No. E0168Ra) was used to perform the SOD assay. All the reagents, samples, and standards were prepared following the manufacturer's procedure. Samples and ELISA reagent were added to each well and incubated for 1 hour at 37°C. The ELISA plate was washed five times, and substrate solutions A and B were added and incubated for 10 minutes at 37°C. A stop solution was added, and the color change was observed. The OD values for each well were read using a microplate reader set up at 450 nm for 10 minutes.

Netrin-1

The Rat Netrin-1 ELISA Kit (MyBioSource, USA) (Cat No. MBS163009) was used in this study. Each well was filled with samples and ELISA reagent and incubated for 1 hour at 37°C. The ELISA plate was then rinsed five times before substrate solutions A and B were added. After 10 minutes at 37°C, the stop solution was added, and the color changed from blue to yellow. Each well OD value was determined using a microplate reader set to 450 nm for 10 minutes.

Apolipoprotein-E

The ApoE levels were measured using the ApoE ELISA Kit (MyBioSource, USA) (Cat No. MBS263133) was used to perform the ApoE levels. The standards, samples, and reagents were well prepared. The well was incubated at 37°C for 90 minutes. The biotinylated antibody solution was prepared and incubated for 30 minutes. The ELISA plate was cleaned twice. Then the biotinylated antibodies were applied to each well. The ELISA plate was cleaned three times more, and the enzyme conjugate was applied to each empty well for 30 minutes at 37°C. The ELISA plate was washed more than five times. The color reagent was added to each empty well and then incubated at 37°C in the dark. The standard turned dark and a color gradient developed. The color reagent C was well mixed into each well and read at 450 nm OD for 10 minutes.

Data analysis

The provided data was analyzed using the SPSS 23.0 software program (IBM Corporation, Armonk, NY). The Kolmogorov–Smirnov and Levene tests were used to determine the normality of the data. The data were examined using a paired *t*-test (pre-and posttest) and an independent test between groups with a confidence interval of *p* < 0.05 to assess the significant difference between treatments. Figures and tables were used to describe the results of the observations. GraphPad Prism 8.0 was used to create the graphical display (GraphPad Software, Inc., San Diego, CA).

RESULTS

Lipid profile

Total cholesterol level

The total cholesterol level of control rats was higher in the pretest than that in the post-test. However, there was no significant difference (*p* > 0.05) between pre- and posttest PSPE rats (Table 1). This suggests that PSPE can maintain total cholesterol levels even when impacted by a high-cholesterol diet (Figure 1).

TG, HDL and LDL levels

The mean TG, HDL, and LDL levels of Wistar rats did not differ significantly (*p* > 0.05) between the groups in the pretest circumstances (Table 2). However, TG, HDL, and LDL levels differed significantly (*p* > 0.05) between the control and PSPE groups (Table 2). Due to high-cholesterol diets, PSPE intervention lowered TG levels, maintained HDL levels, and reduced LDL levels, which eventually resulted in total cholesterol levels that were comparable (Figure 2).

Oxidative stress

MDA and SOD levels

In the pretest conditions, the mean levels of MDA and SOD in rats fed a high-cholesterol diet did not show significant differences (*p* > 0.05). (Figure 3). However, as compared to the control group, there was a significant decrease (*p* < 0.05) in the posttest condition of the treatment group, which was given a combination of high cholesterol and PSPE diet for 3 months (Table 3).

Netrin-1 levels

The investigation found that rats fed a high-cholesterol diet for 3 months had decreased Netrin-1 protein levels. Netrin-1 protein concentration was 111 ng/l in the pretest condition and decreased to 97 ng/l after 3 months on a high-cholesterol diet. The PSPE rats group substantially increased Netrin-1 protein levels (*p* < 0.05). The pretest Netrin-1 protein level in the PSPE group was 82.44 ng/l and increased to 115 ng/l after 3 months of treatment (Table 4). Being compared to the posttest Netrin-1

Table 1. Total blood cholesterol levels before (pretest) and after (posttest) treatment.

Groups	Cholesterol levels ± SD (mg/dl)		
	Pretest	Posttest	<i>p</i> -value
Control	131.33 ± 20.43	261.25 ± 18.74	<i>p</i> < 0.05*
PSPE	133.80 ± 25.52	131.02 ± 4.3	<i>p</i> > 0.05

Note: PSPE: Purple sweet potato extract. Results are presented as mean ± SD. *p*-value was tested by independent *t*-test (pre-and posttest) and independent test between groups with a significant difference at *p* < 0.05.

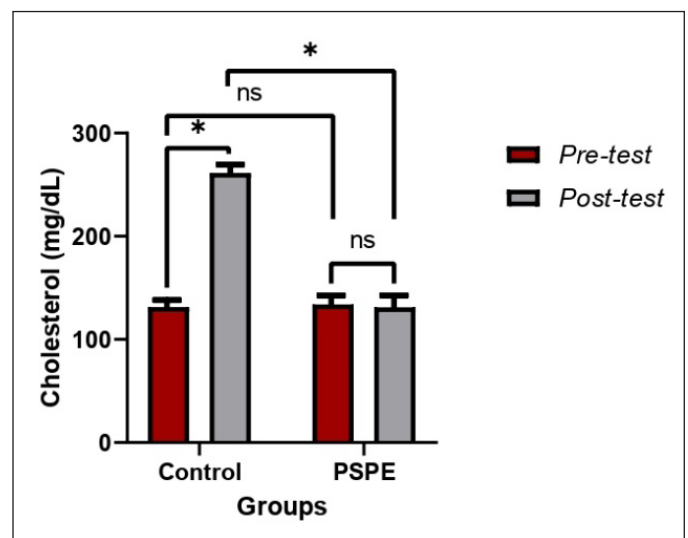


Figure 1. Total cholesterol levels of hypercholesterolemic Wistar rats. Based on the paired *t*-test (pre-and posttest) and an independent test between groups, the * sign indicates a significant difference (*p* < 0.05), whereas NS indicates no significant difference (*p* > 0.05).

Table 2. TG, HDL, and LDL levels before (pretest) and after (posttest) treatment.

Groups	TG ± SD (mg/dl)		HDL ± SD (mg/dl)		LDL ± SD (mg/dl)	
	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
Control	151.69 ± 6.4	151.34 ± 5.0	62.88 ± 4.25	59.79 ± 1.6	149.06 ± 21.41	171.18 ± 19.18
PSPE	148.39 ± 1.9	131.27 ± 1.9	58.55 ± 4.40	86.43 ± 1.9	146.80 ± 25.98	18.33 ± 4.6
<i>p</i> -value	<i>p</i> > 0.05	<i>p</i> < 0.05*	<i>p</i> > 0.05	<i>p</i> < 0.05*	<i>p</i> > 0.05	<i>p</i> < 0.05*

Note: PSPE: purple sweet potato extract. Results are presented as mean ± SD. *p*-value was tested by independent *t*-test (pre-and posttest) and independent test between groups with a significant difference at *p* < 0.05.

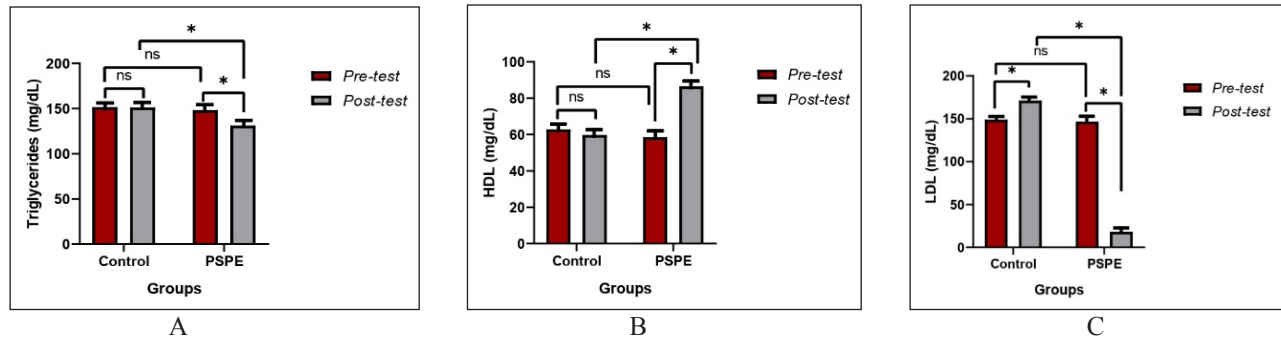


Figure 2. (A) TG, (B) HDL, and (C) LDL levels of hypercholesterolemic Wistar rats. Based on the paired *t*-test (pre-and posttest) and an independent test between groups, the * sign indicates a significant difference ($p < 0.05$), whereas NS indicates no significant difference ($p > 0.05$).

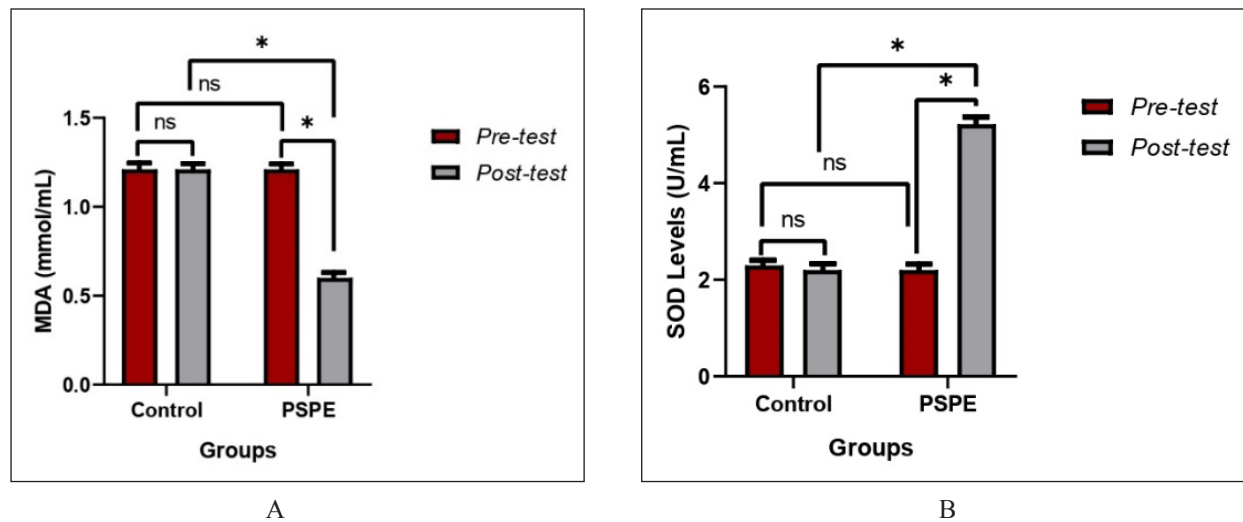


Figure 3. (A) MDA and (B) SOD levels of hypercholesterolemic Wistar rats. Based on the paired *t*-test (pre-and posttest) and an independent test between groups, the * sign indicates a significant difference ($p < 0.05$), whereas NS indicates no significant difference ($p > 0.05$).

protein levels in the control group, these findings demonstrated more significantly increased Netrin-1 protein levels in the PSPE group (Figure 4).

Apo-E levels

In the pretest and posttest conditions, Apo-E levels in the control group showed no significant decrease ($p > 0.05$) even after 3 months of a high-cholesterol diet (Figure 5). Similar to the pretest control conditions, the group of PSPE rats showed a significant increase in Apo-E levels ($p < 0.05$) after 3 months of PSPE treatment (Table 5).

DISCUSSION

The research aimed to examine the antiatherogenic impact of a high-cholesterol diet by consuming PSPE for 3 weeks and investigate the mechanism of reducing lipid profile, Netrin-1 level, and Apo-E level by decreasing oxidative stress biomarkers. The positive impact of PSPE in hypercholesterolemic subjects has not been explored, particularly as indicated by Netrin-1 and Apo-E protein levels. Several sweet potato cultivars, including purple sweet potato, have previously been studied for their chemical and bioactive content, and this raw material has the

Table 3. Comparison of MDA and SOD levels in this study group.

Groups	MDA (mmol/ml)		SOD (U/ml)	
	Pretest	Posttest	Pretest	Posttest
Control	1.21 ± 0.06	1.21 ± 0.05	2.3 ± 0.3	2.2 ± 0.2
PSPE	1.21 ± 0.05	0.6 ± 0.04	2.2 ± 0.2	5.22 ± 0.14
<i>p</i> -value	$p > 0.05$	$p < 0.05$	$p > 0.05$	$p < 0.05$

Note: PSPE: purple sweet potato extract. Results are presented as mean ± SD. *p*-value was tested by independent *t*-test (pre-and posttest) and independent test between groups with a significant difference at $p < 0.05$.

Table 4. Netrin-1 levels in the serum in this study.

Groups	Netrin-1 levels (ng/ml)		
	Pretest	Posttest	<i>p</i> -value
Control	111	97	$p > 0.05$
PSPE	82	115	$p < 0.05^*$

Note: PSPE: purple sweet potato extract. Results are presented as mean ± SD. *p*-value was tested by independent *t*-test (pre- and posttest) and independent test between groups with a significant difference at $p < 0.05$.

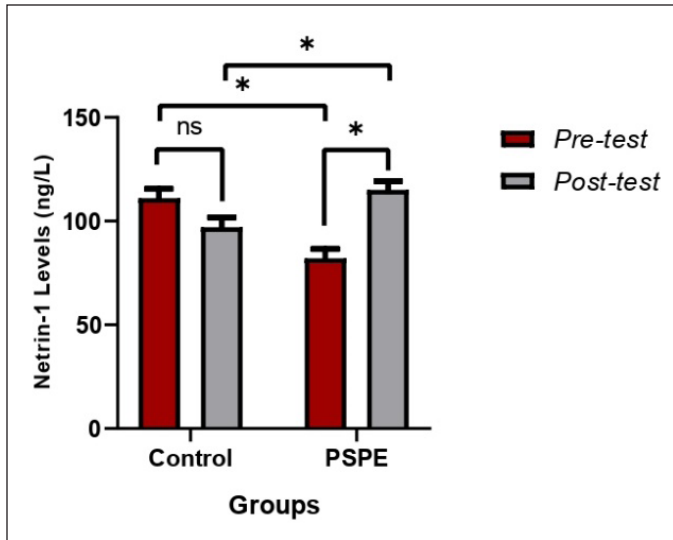


Figure 4. Netrin-1 protein levels in hypercholesterolemic Wistar rats. Based on the paired *t*-test (pre-and posttest) and an independent test between groups, the * sign indicates a significant difference ($p < 0.05$), whereas NS indicates no significant difference ($p > 0.05$).

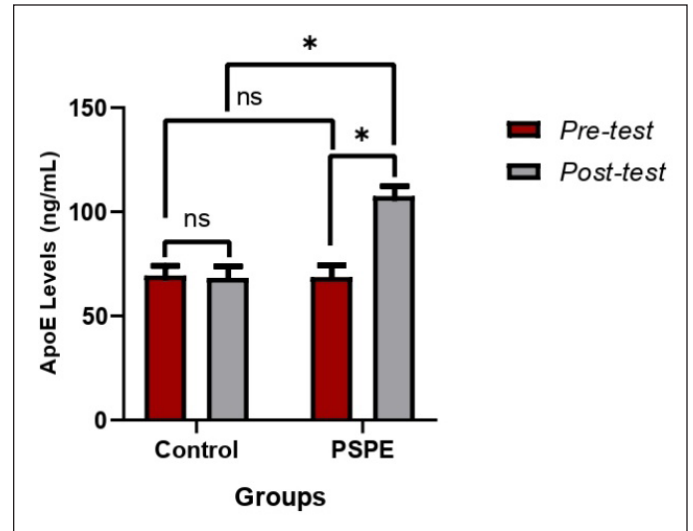


Figure 5. Apo-E levels of hypercholesterolemic Wistar rats based on the paired *t*-test (pre-and posttest) and an independent test between groups, the * sign indicates a significant difference ($p < 0.05$), whereas NS indicates no significant difference ($p > 0.05$).

Table 5. Apo-E levels in this study group.

Groups	Apo-E levels (ng/ml)		
	Pretest	Posttest	<i>p</i> -value
Control	69.43	68.27	$p > 0.05$
PSPE	68.74	107.52	$p < 0.05^*$

Note: PSPE: purple sweet potato extract. Results are presented as mean \pm SD. *p*-value was tested by independent *t*-test (pre-and posttest) and independent test between groups with a significant difference at $p < 0.05$.

potential to be developed as a therapy in both the pharmaceutical and biomedical industries [26].

The findings in this study indicated that PSPE treatment significantly improved the lipid profile and demonstrated effectiveness in the posttest. Rats on a high-cholesterol diet may accumulate body fat by enhancing their lipid profiles and promoting an increase in adipocyte size and quantity [27,28]. Because LDL accounts for 60% of total cholesterol, it is also known as “bad cholesterol” and is a major risk factor for atherosclerosis [29]. More cholesterol will be transported from the liver to peripheral tissues when LDL cholesterol levels increase. As a result of cholesterol accumulating in the blood vessels, atherosclerosis develops [30]. Previous research revealed that PSPE supplementation at a dose of 30% was able to reduce body weight and fat accumulation, improve lipid profiles, and modulate energy expenditure, as well as being able to maintain liver and kidney function in obese rats given a high-fat diet [31]. Related research also revealed that the performance function of PSPE, which was able to induce the expression of AMP-activated protein kinase in the liver, increased type 2 glucose transporter, glucokinase protein levels, and insulin- α receptors significantly in hyperglycemic rats [32].

Previous studies have shown the efficacy of garlic and ginger in reducing dyslipidemia by improving fat metabolism [33,34]. The extracted material stimulates bile acid production, decreasing cholesterol [35]. Our data here show that the decrease

in cholesterol was followed by an increase in HDL in the PSPE groups, a substance known to participate in the reverse cholesterol transport (RCT) process [36]. Interestingly, a previous study had shown that lowering LDL cholesterol by 2 mg/dl could reduce the risk of cardiovascular disease and atherosclerosis by 1% compared to a high-cholesterol diet [37,38]. In contrast to LDL, HDL is referred to as “good cholesterol” and is required for the RCT mechanism to function correctly [39–41]. Consequently, elevated LDL levels can allocate excessive cholesterol from peripheral tissues to the liver for processing [42].

Antihypercholesteromic activity from PSPE is linked to its flavonoid concentration, which is thought to influence the lipid profile by interacting with several enzymes involved in lipid metabolism in the liver [28,38]. Preclinical studies using cell culture and animal models established the role of flavonoids (anthocyanins, anthocyanidins, flavonols, and flavones) in influencing RCT and HDL performance in forms other than essentially regulating HDL cholesterol concentrations by regulating macrophage-derived cholesterol release and hepatic paraoxonase one expression [43]. Furthermore, the consumption of anthocyanin-rich foods was related to significant changes in blood biomarkers associated with HDL function in various human populations (hyperlipidemia, hypertension, and diabetes) in clinical investigations [44,45]. Because of a chemical structure known as delphinidine, anthocyanins improved lipid profiles. The chemical structure of anthocyanin affected TG, LDL, and HDL [46].

Oxidative stress caused by high cholesterol diet also seems to be reduced by PSPE treatment. We hypothesized that PSPE flavonoids protected against oxidative stress, as demonstrated by decreased MDA and increased SOD levels in the PSPE group. Flavonoids can also prevent thrombus formation [47], enhance endothelial function [48], modify lipid levels [49], and regulate glucose metabolism [50]. Consequently, dietary content plays a role in regulating oxidative stress caused by the consumption of oxidants and antioxidants [51]. Thus, atherosclerosis can be reduced by improving endothelial function by administering

cholesterol-lowering drugs or antioxidant treatment. Interestingly, our previous study showed a linear relationship between the dose of flavonoid produced from PSPE and its antihyperglycemic effect in streptozotocin-induced rats [52].

The distribution of the protein Netrin-1 is essential to determine its effect on atherosclerosis development [53,54]. Our finding of an increase in the Netrin-1 protein level after PSPE administration supports the notion that it is required for optimal endothelial function due to the increased serum Netrin-1 levels. In contrast, under oxidative stress situations, particularly, those associated with elevated LDL levels due to high-cholesterol diets may result in reduced endothelial function and lower Netrin-1 levels [10]. According to its function, the protein Netrin-1 inhibits the inflammatory process by preventing monocytes from reaching the endothelium. Thus, decreasing Netrin-1 levels could increase the inflammation caused by monocyte entrance into blood vessels [55]. Thus, Netrin-1 in the artery lumen is atheroprotective, whereas Netrin-1 generated by macrophages on plaque locations causes macrophage retention and smooth muscle cell migration within plaques [1].

Apo-E functions as a ligand for LDL receptors in liver cells, boosting or optimizing blood LDL absorption by liver cells for metabolism [56]. Interestingly, Apo-E inhibits atherosclerosis in hyperlipidemic circumstances by increasing plasma ApoA1-HDL, which is proven to reduce intracellular lipid accumulation, circulating leukocyte activation, and endothelial activation [57]. An increase in Apo-E levels in this study could be associated with a decrease in oxidative stress enzymes such as MDA [58]. These results are supported by previous studies utilizing aged garlic extract, which is capable of slowing down atherosclerotic processes involving inflammatory processes by decreasing serum CRP, XB2, TNF- α , IRAK4 protein levels, and AMP-activated protein kinase activity in the liver in Apo-E-knockout mice [59].

In summary, the findings of this study demonstrate the importance of PSPE with high anthocyanin content in maintaining a healthy lipid profile under normal conditions, consistent with previous research. Purification of bioactive compounds and other components is necessary to ascertain whether bioactive substances function in atherosclerosis. The reduced oxidative stress improves endothelial function and higher Netrin-1 synthesis by the endothelium. These findings suggest that PSPE supports the protein Netrin-1 in circulation as a protective endothelium, particularly in reducing inflammation and avoiding atherosclerosis.

CONCLUSIONS AND FURTHER RESEARCH

This research demonstrates that PSPE has antiatherogenic properties. It has been shown to regulate the lipid profile, decrease oxidative stress by lowering MDA levels and boosting SOD levels, and increase Netrin-1 and Apo-E protein levels in rats given a high-cholesterol diet for 3 months. We suggest that supplementation with 200 mg/ml PSPE with a healthy diet may help to control atherogenesis and might be developed as a dietary supplement.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

The Research Ethics Committee of the Faculty of Medicine, Udayana University, had approved this research protocol with approval No. 2021.03.1.1078, dated 07/12/2021.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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