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Short Communication

Evaluation of *In Vivo* Anti-dyslipidemic Activity of the Combination of *Andrographis paniculata* Extract (APE) and *Ipomea batatas* Leaf Extract (IBE)

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ABSTRACT

Andrographis paniculata and *Ipomea batatas* are widely found in Indonesia, either wild or cultivated. Both plants contain some bioactive compounds, mainly andrographolides and anthocyanins. These compounds possess blood lipid reducing property through their ability to lower total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C) and increase high-density lipoprotein cholesterol (HDL-C) levels. The purpose of this study was to evaluate the potential anti-dyslipidemic potency of the combination of *Andrographis paniculata* Extract (APE) and *Ipomea batatas* Leaf Extract (IBE) in rats. Plants were extracted, and the levels of andrographolide and total flavonoid content (TFC) from each extract were measured. The extracts were administered to the dyslipidemic rats. The blood lipid levels and histopathology of the aortic organs were observed. The obtained data were analyzed statistically with one-way ANOVA and with the biplot and multivariate analysis. The results showed that the APE, IBE, APE, and IBE combinations improved the blood lipid profiles and prevented fatty plaque accumulations in rat aortas. The anti-dyslipidemic ability may be due to the presence of andrographolide and flavonoid compounds in the extract. The correlation matrix plot analysis showed a linear relationship to the lipid profile of all treatment groups. Multivariate analysis of anti-dyslipidemic activity can help determine the most optimal effect in lowering blood lipid levels. The combination of APE and IBE provides the most optimal activity because it decreases TC and LDL-C. This combination has a protective effect on the aorta, thereby preventing atherosclerosis.

Keywords: Anti-dyslipidemic, *Andrographis paniculata*, combination, extract, *Ipomea batatas*

Introduction

Dyslipidemia is a condition of abnormal blood lipid levels in the form of total cholesterol (TC), triglyceride (TG) levels, low-density lipoprotein (LDL-C) above normal values and high-density lipoprotein (HDL-C) levels below normal values.[1] Levels of TC, TG and LDL-C that exceed normal limits, while the level of HDL-C that is below normal limit will trigger diseases such as diabetes mellitus, atherosclerosis, stroke, hypertension, and cardiovascular disorders.[2] Several factors cause a rise in TC, TG and LDL-C levels and cause a decline in HDL-C levels; one of such factors is diet. Fat-rich diets are one of the triggering factors for dyslipidemia.[2] *Andrographis paniculata* is a plant that has the potential to reduce lipid levels in the blood. Andrographolide is a lactone terpene compound in *Andrographis paniculata* and is responsible for the pharmacological activity of *Andrographis paniculata*, one of such activity is antihyperlipidemic activity.[3-5] Apart from andrographolide, flavonoids are class of compounds that can reduce hyperlipidemia.[6] One of the plants that grow in Indonesia that contain anthocyanins; a type of flavonoid compounds is *Ipomea batatas*.[7]

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The present research studied the combined effect of *Andrographis paniculata* extract (APE) and *Ipomea batatas* leaf extract (IBE) as anti-dyslipidemic agent. The goal was to get the best combination of APE and IBE with anti-dyslipidemic activity. APE and IBE optimal combination is expected to help improve blood lipid profile and protect against aortic atherosclerosis. First, the content of andrographolide and total anthocyanin contents in each extract was measured. Then the ability of the combination of *APE* and *IBE* to reduce blood lipid levels was evaluated.

Materials and Methods

Materials

Analytical grades 96% ethanol (Bratacho, Bali), hexane (Bratacho, Bali), KCl (Bratacho, Bali), CH_3COONa (Bratacho, Bali), Andrographolide (Sigma-Aldrich), vitamin D3 1.0 MIU/g (DSM Nutritional Ltd.), chloroform (Merck, Germany), methanol (Merck, Germany), calcium (Bratacho, Indonesia), cholesterol FS (Diasys), triglyceride-FS (Diasys), low-density lipoprotein precipitant (Diasys), high-density lipoprotein precipitant (Diasys), silica gel TLC plate GF 254 nm (Merck) were purchased from PT Kurnia Jaya Sentosa, Surabaya, Indonesia. The equipment used consisted of a Rotary evaporator (Heidolph), UV-Visible spectrophotometer (Shimadzu), the light microscope (Olympus Corporation, Tokyo, Japan).

Plant collection

Andrographis paniculata and *Ipomea batatas* leaves were freshly harvested from Aan Village, Klungkung Regency, Bali Province (8.509013°S 115.380522°E), Indonesia, in December 2019. The plants were authenticated at the Indonesian Institute of Sciences Botanical

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Garden Conservation Center, Eka Karya Bali with document no: B-1488/IPH.7/AP/XII/2019.

Extraction
Andrographis paniculata leaves (1 kg) were sorted, washed and cut into small pieces. Further, the *Andrographis paniculata* leaves were steamed for 15 minutes, then macerated with 5 L of 96% ethanol for 24 hours.
Ipomea batatas leaves (1 kg) were sorted, washed and cut into small pieces. Further, the *Ipomea batatas* leaves were steamed for 15 minutes, then macerated with 5 L of 96% ethanol: 3% acetic acid (85:15) solvent mixture for 24 hours.

Determination of andrographolide content in APE
The TLC spectrophotodensitometric method was used to determine the andrographolide content in the extract. The andrographolide standard was made at varied concentrations; 80; 100; 120; 140; 160; 180; 200 µg/mL. The regression equation was obtained by plotting AUC vs concentration. Andrographolide content in APE was determined from the standard plot.

Determination of Total Anthocyanin Content (TAC) in APE and IBE
The total anthocyanin content was determined by the pH difference method. Samples were dissolved in KCl buffer pH 1.0 and CH_3COONa buffer pH 4.5. The absorbance of the solutions was read at 510 nm and 700 nm. The final absorbance and Total Anthocyanin Content (TAC) were calculated using the equation below:

$$A = (A_{510} - A_{700})pH1{,}0 - (A_{510} - A_{700})pH4{,}5$$

$$Total\ Anthocyanin\ \left(\frac{mg}{L}\right) = \frac{AxMWxDFx1000}{lx\varepsilon}$$

Where:
A = (A510-A700) pH 1.0 - (A510-A700) pH 4.5
ε = molar absorptivity of 3-glucose cyanidine (26,900 (L x mol –1 x cm –1))
MW = molecular weight of 3-glucose cyanidine (449.2 g / mol)
DF = dilution factor
l = Thickness of the cuvette (1 cm)[8]

Animal induction
The *in vivo* anti-dyslipidemic evaluation was carried out using male Wistar rats. Forty-two (42) male Wistar rats aged between 6-8 weeks and bodyweight ranged from 150 – 250 g. The rats were conditioned for seven days by adjusting the temperature, humidity and light. Prior to the experiment, ethical clearance for the use of laboratory animals was obtained with document no: 68/UN14.2.9/PT.01.04/2020. The rats were grouped into seven groups of six rats per group. The dyslipidemic state was obtained by giving an atherogenic diet (combination BR1 standard: duck egg yolk: lard = 85: 5: 10; 200,000 IU vitamin D3; calcium). Dyslipidemia was induced in the rats for 60 days and continued until day 90 during treatment (30 days). The groupings, diet and extracts administration are as shown in Table 1 below.

Measurement of Lipid Levels
The fasting blood lipid profiles were determined twice, on the 60th day (sixty days after induction with fat-rich food) and the 91st day (thirty days after receiving the treatment). The levels of TC, TG, LDL-C and HDL-C of rat's serum were measured using enzymatic reactions.[9]

Atherogenic Index of Plasma (AIP)
The AIP is a logarithmic ratio of TG and HDL-C (TG/HDL-C). High TG value or low HDL-C value will produce a high AIP value.

Histopathology of the Aortic Organs
Rats' aortas were evaluated by histopathological method. The aortas were fixated in 10% of neutral buffered formalin solution, fixated aorta tissues were embedded in paraffin wax, cut into 4 µm thick sections, stained with hematoxylin and eosin (H&E), and observed under a light microscope to assess the condition of the aortas. The slides were analyzed under the light microscope (Olympus BX63 with a DP72 camera, Olympus Corporation, Tokyo, Japan) at 400 × magnification. Sections were observed for vascular congestion, inflammation and scored. The aortas were scored as follows: 0 for normal aorta; 1 for the widening of the constituent cells of the aorta; 2 for fragmentation of elastic fibres and foam cells; 3 for smooth muscle cell proliferation; and 4 for ulceration or calcification of lipid plaques.[3,9]

Statistical analysis
The obtained data and aorta scores were analyzed using SPSS software for windows to determine whether significant differences occurred before and after APE, IBE, and combination administration. The normality of the data distributions of each variable was statistically analyzed using Kolmogorov–Smirnov test. The data were expressed as average ± standard deviation (SD) and examined for their statistical significance of difference with ANOVA and LSD t-test. P-values of less than 0.05 ($p < 0.05$) were considered to be statistically significant. A correlation matrix analysis was utilized to assess the correlation between groups of all tested lipid profile parameters (TC, TG, LDL-C and HDL-C). Meanwhile, PCA Biplot (Principal Component Analysis Biplot) were used to assess the contribution of each lipid profile parameter.

Results and Discussion

Compound content
APE and IBE contain some chemical compounds such as andrographolide and anthocyanin. These potentially active compounds were used to determine the concentration of APE and IBE given to the test animals. APE contains 9.6 mg of total andrographolide in one gram of extract. IBE contains 95.28 mg of total anthocyanins in one gram of extract (TAC is equivalent to 3-O glycoside compounds). Total flavonoids in APE and IBE were 59.5 µg/mL and 674.83 µg/mL, respectively.

Table 1: Diet and extract administration

Group	Induction/Treatment
Group 1 (Normal control)	Rats fed with standard diet and sufficient amount of water
Group 2 (Atherogenic control)	Rats fed with atherogenic diet and sufficient amount of water
Group 3 (Athorvastatin)	Rats fed with atherogenic diet, athorvastatin 7.2 mg/kg body weight and sufficient amount of water
Group 4 (AE)	Rats fed with atherogenic diet, APE 300 mg/kg body weight and sufficient amount of water
Group 5 (IE)	Rats fed with atherogenic diet, IBE 2 mL/rat and sufficient amount of water
Group 6 [AE (150) + IE (1)]	Rats fed with atherogenic diet, APE 150 mg/kg body weight, IBE 1 mL/rat and sufficient amount of water
Group 7 [AE (300) + IE (2)]	Rats fed with atherogenic diet, APE 300 mg/kg body weight, IBE 2 mL/rat and sufficient amount of water

Pharmacological activity

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Atherogenic diets were proposed to elevate the blood lipid levels in rats. Atherogenic feeding was consecutively given for 60 days (Figure 2A-i). An atherogenic diet can increase TC, TG, LDL-C levels but decrease HDL-C levels in the blood. The parameters were significantly different from the normal control group ($p < 0.05$). Atherogenic feeding also cause some changes in the rats' aortic morphology. While the normal aorta (Figure 2C-1); score = 0) had normal morphology. Rats that received an atherogenic diet experienced morphological changes such as the dilation of cells comprising the aorta tunica intima (Figure 2C-2; score = 1).

Longer duration of the atherogenic feed administration, caused foamy cell formation (Figure 2C-3; score = 2), smooth muscle cell proliferation on the aorta tunica intima in all animals (Figure 2C-4; score = 3). Atherogenic feeding was continued throughout the treatment administration. The treatment was carried out for 30 days (from day 61 to day 90), except for the normal and atherogenic groups. Administration of atorvastatin, APE, IBE, APE (150) + IBE (1), APE (300) + IBE (2) were able to reduce blood lipid levels (Figure 2 A-ii).

Administration of APE, IBE and a combination of APE and IBE reduced blood lipid levels and showed that they were not significantly different ($p > 0.05$). Likewise, the administration of APE (150) + IBE (1) and APE (300) + IBE (2) showed no different results. Furthermore, the prediction of heart problems, was indicated by the AIP score. AIP is a logarithmic ratio of TG and HDL-C (TG/HDL-C). The AIP value calculated in the treated rats compared to the normal and atherogenic control groups showed that administration of APE, IBE, APE (150) + IBE (1), APE (300) + IBE (2) was able to cause the AIP value not to differ significantly from the AIP value of normal rat. This suggest that the treatment has the potential to reduce the risk factors for cardiovascular disorders. AIP has a positive correlation with the risk of cardiovascular disorders.

The atherogenic diet was fed to the rats for 90 days. This caused changes in rats' aorta morphology, which was shown by a score of 3, experienced by 83% of the total tested animals, a score of 2, experienced by 17% of the total tested animals. Rats treated with APE, IBE and their combination had the same score; 67% out of the total tested animals had 0 scores, while 33% out of the total tested animals had score 1 (Figure 2 B-i). Atherosclerosis scores were analyzed by comparing atorvastatin, APE, IBE, APE (150) + IBE (1), APE (300) + IBE (2) groups to the normal group, and there were no statistically significant difference. Rats that were administered the combination of EPA and IBE have the same potency with a single administration. Furthermore, there was no elevation in their potency even though the number of combinations of APE and IBE was increased.

Several epidemiological studies stated a relationship between high TC, TG, LDL-C and low HDL-C levels in the blood and atherosclerosis.[10] AIP is an early prediction of the possibility of atherosclerosis. The atherogenic index of plasma (AIP), the logarithmic transformation of the TG level to the HDL-C level ratio, is designated as a new marker in atherosclerosis risk.[11] Many epidemiological studies have shown a direct relationship between lipid disorders, particularly elevated TC and LDL-C levels, and the risk of coronary artery disease (CVD).

There is a causal relationship between blood lipids and atherosclerosis. High levels of LDL-C have a positive correlation with the occurrence of atherosclerosis, in contrast to the negative correlation for HDL-C. High levels of HDL-C in the blood protect the arteries against atherosclerosis.[12] High blood LDL-C level (hyperlipidemia) triggers LDL oxidation which forms ox-LDL in the arterial intima. ox-LDL will stimulate the formation of atherosclerotic lesions by forming macrophage foam cells (MFCs). MFCs play a critical role in the growth of atherosclerosis, and the emergence of MFCs is the hallmark of the early phase of atherosclerotic lesions.[13] Fatty plaques formation in the arterial intima stimulates activation of NFk-B, which is not present in normal arterial conditions. Atherosclerotic lesions formation leads to upregulation of NFk-B, and activated NFk-B will recruit mononuclear leukocytes into the arterial intima, which is a significant phase of atherosclerosis, which is characterized by increased levels of other proteins such as vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), E-selectin, and chemokines interleukin 8 (IL-8).[14-16] ox-LDL induces increased expression of vascular cell adhesion molecule-1 (VCAM-1); the key adhesion molecules for monocytes and T cells, in the endothelial surface overlying the main artery.[17] inhibition of HMGCoA reductase activity is a major limitation in the cholesterol biosynthetic pathway, leading to a significant reduction in VLDL-C production by the liver, upregulation of hepatic LDL receptors and consequently removal of LDL-C from the blood circulation.[18] In this study, the administration of APE, IBE, APE (150) + IBE (1) and APE (300) + IBE (2) was able to cause the AIP value not to differ significantly from normal controls (Figure 2 B-ii). AIP value increased accordingly because treatment with APE, IBE, APE (150) + IBE (1), APE (300) + IBE (2) was able to reduce TG levels significantly and was able to increase HDL-C levels in the rats (Figure 2 A-ii). Andrographolide was able to inhibit the formation of ox-LDL; hence the foam cells was not formed, which causes atherosclerotic lesions not to occur. Andrographolide depending on the dose attenuates ox-LDL-induced MFCs formation and lipid accumulation.[19]

A linear relationship in the blood lipid parameters (TC, TG, HDL-C and LDL-C) was presented by correlation matrix plot (Figure 3.A). The results of the analysis showed that the administration of a single extract of APE had a strong correlation with IBE ($p < 0.001$) and with the administration of the combined extract of APE (150) + IBE (1), APE (300) + IBE (2). However, administration of the extract combination APE (300) + IBE (2) had a weak correlation with the extract combination APE (150) + IBE (1) (Figure 3A). The analysis results using the R Studio correlation matrix indicated that it is better if the extract was given as a single APE or IBE than the combination as APE (150) + IBE (1). Analysis with the biplot PCA showed that LDL-C was influenced by combining APE (150) + IBE (1). Meanwhile, TG was influenced by APE (300) + IBE (2). APE and IBE acted conversely in their effects on both HDL-C and TC (Figure 3B). The combination of extracts APE (150) + IBE (1) and APE (300) + IBE (2) were able to reduce TC and LDL-C levels.

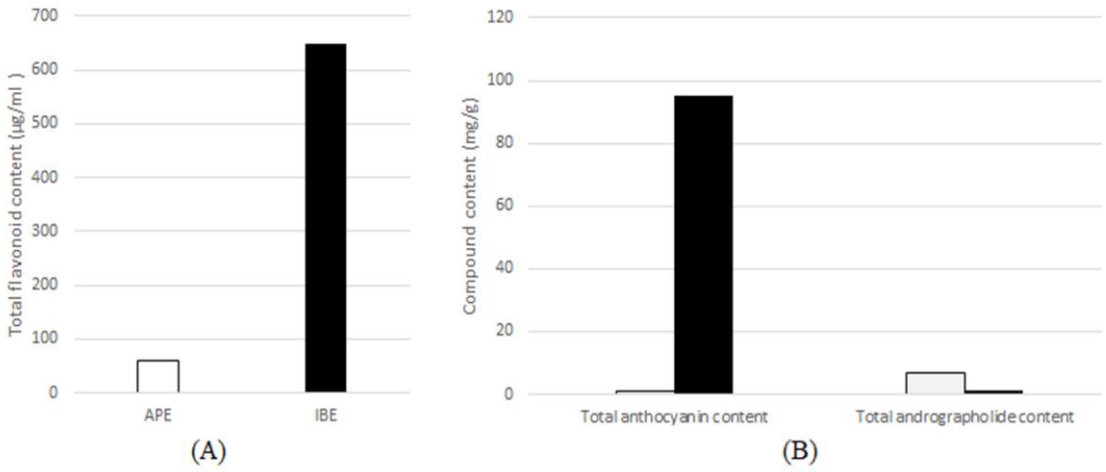

Figure 1: Quantitative analysis of TFC (A), TAC and andrographolide (B) from APE and IBE

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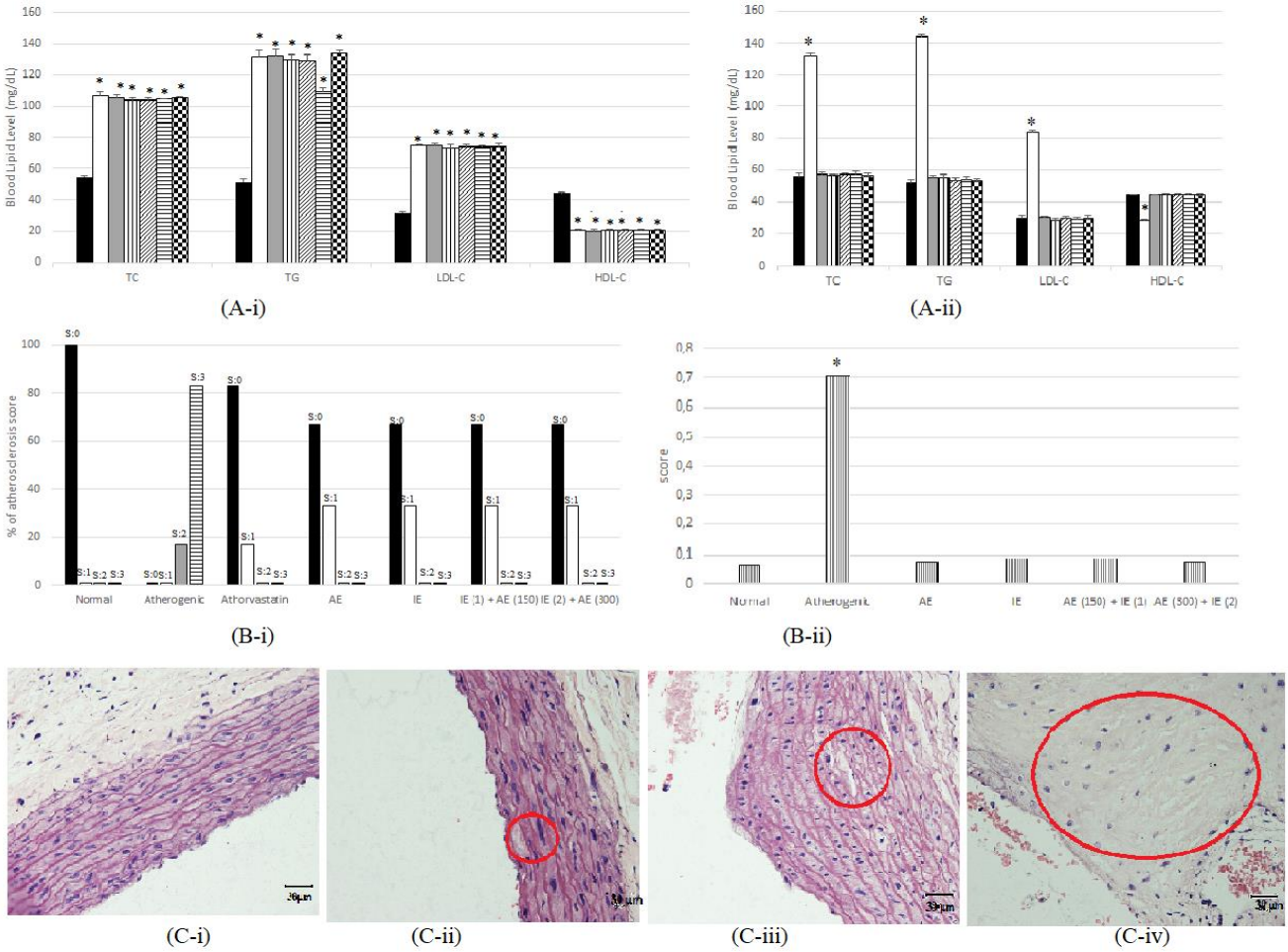

Figure 2: The process of atherosclerosis on rat's aorta, magnification 400x (A), the blood lipid profile of rat after induced dyslipidemic (B-1) the blood lipid profile of rat treated with anti- dyslipidemic (B-2), AIP score (C-1), and aorta scoring morphology of rat's aorta on treated with anti- dyslipidemic or preventive atherosclerosis (C-3).
(B-i, ii): Blood lipid profile; ■ = normal; □ = atherogenic; ■ = athorvastatin; ▥ = AE; ▨ = IE; ▬ = AE (150) + IE (1); ▀ = AE (300) + IE (2); (B-iii): aorta scoring morphology of rat's aorta preventive atherosclerosis; S:= score.

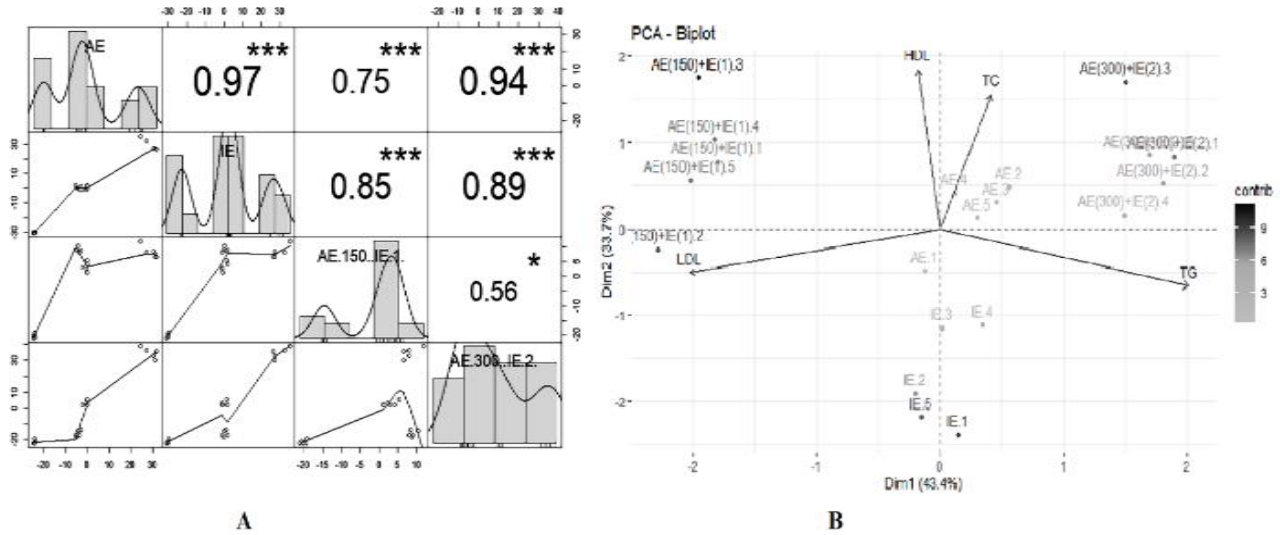

Figure 3: (A) Lipid blood response-group correlation. All of the groups showed high linerity and significant correlation, the administrations of APE, IBE, APE (150) + IBE (1) and APE (300) + IBE (2) had an effect on the lipid profile of rat, *** = not significantly different $p < 0.001$, ** = not significantly different $p < 0.01$ (B) PCA biplot lipid blood response-group correlation

Extract administration showed a positive correlation with the atherosclerosis score. The administration of APE, IBE, APE (150) + IBE (1), and APE (300) + IBE (2) was able to cause a low rat atherosclerosis score which means that there is no significant change in aortic morphology (Figure 2 B-i). The formation of MFCs was influenced by inflammatory factors and the strong anti-inflammatory activity of andrographolide. We suspect that andrographolide could prevent ox-LDL-induced MFCs formation. The results indicated that APE contains andrographolide compounds which can reduce the accumulation of lipids induced by ox-LDL in MFCs, indicating that andrographolide can prevent atherosclerosis. IBE contains total flavonoid compounds, one of which is anthocyanin. Anthocyanins are a type of flavonoid found in purple sweet potato tuber that can inhibit cholesterol absorption in the gastrointestinal tract and presumably impede cholesterol synthesis by the liver.[20] Anthocyanin and andrographolide compounds can inactivate NFk-B so that the pathogenesis of atherosclerosis does not occur.[21-23]

Conclusion

The administration of a single extract of APE, IBE, a combination of extracts of APE (150) + IBE (1), APE (300) + IBE (2) was able to change the lipid profile of rat blood and enhance the condition of rats' arteries. There were no significant differences among each group. The output of multivariate analysis indicated that the combination of AE (150) + IBE (1) gave the optimal effect in reducing blood lipid levels.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Declaration

The author hereby declares that the work presented in this article is genuine and that any liability for claims relating to the content of this article will be borne by them.

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