Comparison of Purple Passion Juice (*Passiflora edulis var. edulis*) and Simvastatin on Lipid-lowering Effect of Hyperlipidemic Rats Model

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Abstract: Hyperlipidemia is a lipoprotein metabolic disorder characterized by high cholesterol and triglycerides in blood circulation. Non-pharmacological management efforts by consuming healthy foods are often the first choice. In the previous research, we found the antihypercholesterolemia potential of purple passion juice 4.2 mL/200gBB/day in experimental animals. This study aims to compare purple passion juice's effectiveness to Simvastatin in improving the lipid profile of the hyperlipidemic rats model. This true experimental study used 32 male Wistar rats, divided into 4 groups: K1 (normal control), K2 (hyperlipidemia control), K3 (purple passion juice 4.2 mL/200gBB/day), K4 (simvastatin 0.18 mg/200gBB/day). We used pork oil six mL/200gBB/day and Propylthiouracil (PTU) 12.5 mg/day, divided into two doses, for 14 days, by gavage, to induced hyperlipidemia. Blood sampling through retro-orbital veins was carried out at the end of induction (pre-test) and the end of the study (post-test) to measure the lipid profile. T-paired test on total cholesterol and triglyceride levels of the pre-post test showed a significant decrease in total cholesterol levels in K4 ($p=0.00$) and a significant decrease in triglyceride levels K3 ($p=0.03$), while in K1, there was a significant increase in both parameters. HDL levels decreased significantly in all groups. There was a significant difference in the one-way ANOVA test for both total cholesterol and triglyceride levels ($p <0.05$). Post Hoc test on post-test total cholesterol levels showed a significant difference in K2 v.s K4 (0.00), but there was no difference between K3 v.s K4 ($p=0,54$). The study concludes that Simvastatin was more effective in reducing total cholesterol levels; however, purple passion juice is more effective in lowering triglyceride levels.

1 INTRODUCTION

Cholesterol and triglycerides are the main lipid components in the blood circulation (Harikumar et al., 2013). Their normal blood circulation levels play an essential role in normal physiological processes (Abumrad and Davidson, 2012). Increasing levels of these lipid compounds in the circulation are known as hyperlipidemia (Harikumar et al., 2013). Lifestyle changes and high calorie, saturated fat, and cholesterol-rich diet cause this condition (Arsana et al., 2019). The increase in these compounds in the circulation can lead to the formation of free radicals, initiate cellular damage, and play a role in atherosclerosis's pathophysiological process (Harikumar et al., 2013; Nghiem-rao, Mavis and College, 2014). Management of hyperlipidemia requires a comprehensive strategy: pharmacological and non-pharmacological therapy. Pharmacological therapy uses anti-lipid drugs, including Simvastatin, a statin group, as the first-line drug. On the other hand, non-pharmacological treatment is often the first choice through a healthy lifestyle by consuming foods and fruits high in antioxidants, phytosterols, low calorie, and rich fibre (Arsana et al., 2019). The indigenous systems of medicine have provided

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extensive plant data for the treatment of hyperlipidemia. Various studies on local natural fruits and plants, among others, have proven their effectiveness in treating it (Harikumar et al., 2013; Alam and Mishra, 2017).

Indonesia is a country rich in various tropical fruits, which are beneficial for health. Although scientifically not confirmed about its efficacy, the practice of using this plant material is widely used as a preventive or first treatment (Barbalho et al., 2012; Maqbool et al., 2019). This is based on the general belief that using these natural ingredients is free from side effects and is readily available in the surrounding environment (Kaur, Jasvir; Kaur, Satvinder; Mahajan, 2013). According to the World Health Organization (WHO), about 80% of the world's population, especially developing countries, use this plant to get it (Soares et al., 2012; Alam and Mishra, 2017). In line with the high public interest in the use of natural ingredients, the scientific community, through their research and publication, has demonstrated the beneficial health effects of consuming this plant due to its phytotherapeutic properties (Matsui et al., 2010; Barbalho et al., 2012; Soares et al., 2012).

Purple passion fruit (Passiflora edulis var. Edulis Sims) is a tropical fruit that has been successfully developed in many countries in the world, including Indonesia. This native Brazilian plant, easy to cultivate and grow in our environment but is often not used because of its sour taste. In fact, behind the taste, this tropical fruit is rich in nutritional and phytochemicals components, making this exotic fruit has a beneficial health value. Based on research, purple passion fruit contains fibre, minerals, phenolic and ascorbic acids (Ramaiya et al., 2019). In Indonesia, research and publications regarding the health benefits of this fruit are still limited.

Previous research has studied the potential of various parts of the passion fruit plant as a herbal medicine source. These studies included the effect of the rind on the maintenance of glycemia (Barbalho et al., 2012), mesocarp in reducing hypercholesterolemia (Corrêa et al., 2014; Ostrowski et al., 2015), fruit peel in cases of asthma (Ross et al., 2008), and also leaf extract as antidiabetic (Kanakasabapathi and Gopalakrishnan, 2015). Exploring the potential of passion juice as an antihypercholesterolemic agent has also been carried out in previous studies (Damasceno et al., 2011; Maricelma da Silva Soares de Souza, Sandra Maria BArbalho, Debora Christina Damasceno, Marilza Viera Cunha Rudge, Kleber Eduardo de Campos, 2012). In the previous study, we found the antihypercholesterolemia potential of purple passion juice (Muntafiah, Ernawati, et al., 2017). Through the previous research, purple passion juice at a dose of 4.2 mL/200gBB/day significantly reduced blood cholesterol levels in experimental animals (Muntafiah, Ernawati, et al., 2017). Continuing the previous research, still focusing on purple passion juice, in this study, we wanted to report the effectiveness of anti-hypercholesterolemia potential of purple passion juice compared to the standard drug, Simvastatin.

2 MATERIALS AND METHODS

2.1 Subjects

This true experimental study used 32 white male rats (Rattus norvegicus) Wistar, 2-3 months old, and 125-250 gr weight. The animals were obtained from the Laboratory of Pharmacology and Experimental Animals at Jenderal Soedirman University, Purwokerto. The animals were kept in an environment with a temperature of 22 ± 2 ° C, 50% humidity, and a light-dark cycle for 12 hours (Sambodo et al., 2019). They were acclimatized for seven days, placed in individual cages with the same material, shape, and size, received AD II pellet and aquadest ad libitum. They were divided into four (4) groups: normal control (K1), hypercholesterolemia control (K2), treatment with purple passion juice 4.2 mL/200gBB/day (K3), and treatment with Simvastatin 0.18 mg/200gBB/day (K4).

2.2 Hypercholesterolemia Induction

Induction of hypercholesterolemia was carried out after the acclimatization period to the K2, K3, and K4 groups. We used pork oil six mL/200gBB/day and propylthiouracil (PTU) 12.5 mg/day dissolved in 1 mL of water, divided into two doses, by gavage. Induction was carried out for 14 days (Kusumastuty, 2014; Muntafiah, Ernawati, et al., 2017).

2.3 Purple Passion Juice Preparation

Fresh purple passion juice is obtained from Pulisen, Boyolali, Central Java. Purple passion fruit is washed, cut into two parts, and the pulp is taken, then squeezed with a filter cloth to separate the juice from the seeds. Making purple passion juice is done every day to obtain fresh juice (Muntafiah, Pratama and Ati, 2019).

2.4 Blood Sampling

Blood samples were collected through the retro-orbital vein using a hematocrit pipette. Before sampling, the animals have fasted for 10 hours. During this time, the experimental animals were still given aqua dest ad libitum. Blood sampling was carried out twice, a pre-test (after induction of hypercholesterolemia) and post-test (end of research). Furthermore, the sample was inserted into a non-EDTA tube, centrifuged, and serum was taken.

2.5 Variable Measurement

Examination of lipid profile (total cholesterol, triglycerides, HDL) was carried out at Biochemistry Laboratory, Faculty of Medicine UNSOED, Purwokerto. Total cholesterol levels were examined using the CHOD-PAP method, using the Dyasis kit. Triglyceride levels were analysed using Glycerol-3 Phosphate-Oxidase (GPO) method, while HDL levels were analysed using the CHOD-PAP method. The sample was examined with a photometer 5010 (Robert Riele GmbH & Co KG, Germany) at a wavelength of 540 nm (Muntafiah, Ernawati, et al., 2017).

2.6 Data Analysis

Data analysis was carried out quantitatively. Data distribution was tested with Shapiro Wilk, and Levene tested the homogeneity of the data. A paired t-test was conducted to compare the mean of the pre-post test of total cholesterol, triglyceride, and HDL levels in each group—the One Way Anova test was conducted to compare the mean levels of parameters tested between groups. One Way ANOVA test was significant if it was obtained p <0.05 and continued with post Hoc LSD.

3 RESULTS

3.1 Animal Weight

Weight measurements were carried out five times during the research period. The first measurement was carried out at the beginning of acclimatization, whereas the second was carried out before the induction. The third measurement was then filled after hypercholesterolemia induction/before treatment followed by the fourth measurement, which carried out in the first week of treatment. The final measurement was taken at the end of the research. The average body weight of experimental animals during the research period is presented in Figure 1.

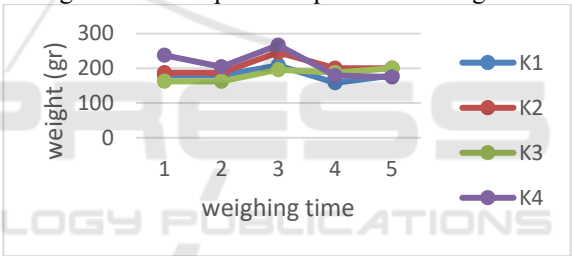

Figure 1. Bodyweight of the Mice.

Table 1. Lipid profile of the animal model.

Lipid profile	Groups			
	K1	K2	K3	K4
Total cholesterol (mg/dL)				
pre-test	67.5 ± 7.42[a]	125 ± 19.35[b]	104.67 ± 20.32[b]	133 ± 29.79[b]
post-test	113.00 ± 21.79[a]	110.5 ± 16.82[ab]	84.17 ± 16.12[b]	79.67 ± 11.38 [b]
delta*	45.5	-14.4	-20.50	-53.33
p pre-post **	0.00	0.20	0.05	0.00
Triglycerides (mg/dL)				
pre-test	61.67 ± 18.81[a]	215 ± 88.95[b]	261 ± 96.17[b]	176.67 ± 102.83[b]
post-test	186.83 ± 70.24[a]	161.17 ± 34.44[a]	139.67 ± 28.92 [a]	157.33 ± 45.89[a]
delta*	125.16	-53.83	-121.33	-19,34
p pre-post **	0,02	0,25	0,03	0,6
HDL (mg/dL)				
pre-test	85.33 ± 41.10[a]	109.33 ± 24.41[a]	79.67 ± 23.13[a]	82.17 ± 14.46[a]
post-test	46.17 ± 8.57[a]	51.33 ± 13.49[a]	48.67 ± 9.22 [a]	37.5 ± 9.29 [a]
delta*	-39.16	-58	-31	-44.67
p pre-post **	0,054	0,00	0,03	0,00

* Delta (the mean difference between pre-test and post-test, positive indicates an increase, negative indicates a decrease.
** p<0,05 in each column shows a significant difference between pre-test and post-test.
[a,b] Different notations on the same line indicate significant differences.

3.2 Lipid Profile

Based on Table 1. we can see that the normal control group (K1) had a mean total cholesterol level of 67.5 mg/dL, triglycerides 61.67 mg/dL, and HDL 85.33 mg/dL. Hyperlipidemia induction using pork oil and propylthiouracil in the K2, K3, and K4 groups, significantly increased the total cholesterol and triglyceride levels. T-paired test on pre-post test total cholesterol levels showed a significant decrease in K4 groups. On the other hand, in the normal control group, there was a considerable increase. Likewise, for triglyceride levels, the paired t-test showed a significant decrease in triglyceride levels only in K3, while in K1, there was a considerable increase.
Meanwhile, HDL levels decreased significantly in all groups. One Way ANOVA test was carried out on pre-test total cholesterol and triglyceride levels (after hypercholesterolemia induction) showed a significant difference in the mean levels of total cholesterol and triglycerides ($p < 0.05$). Furthermore, the post hoc test results showed a significant difference between K1 and K2, K3 and K4 (this indicates the success of hypercholesterolemia induction). Furthermore, one Way ANOVA test for total cholesterol and triglyceride levels showed a significant difference ($p < 0.05$). Post Hoc test on cholesterol levels showed a significant difference ($p < 0.05$) in K2 v.s K4. However, there was no difference between K3 v.s K4 ($p = 0.54$).

4 DISCUSSION

A high-fat diet is directly linked to hyperlipidemia in humans. To test the herbal effect on reducing circulating lipids, an experimental study was carried out with an experimental animal model of hyperlipidemia in the laboratory (Leite Matos et al., 2005). Animal models used to identify herbal remedies' effectiveness can mimic human pathophysiology (Briggs et al., 2014). In this study, we made an experimental animal model of hyperlipidemia. Hyperlipidemia induction was done by giving pork oil six mL/200gBB/day (Kusumastuty, 2014) and propylthiouracil (PTU) 12.5 mg/day for 14 days (Untari and Pramukantoro, 2020) by gavage. This induction technique can increase total cholesterol and triglyceride levels in Wistar rats. Based on this research, in the regular control group, the mean total cholesterol was 67.5 mg/dL, and the average triglyceride level was 61.67 mg/dL. According to the reference, this average level states that the range of normal total cholesterol levels for experimental animals rats aged 8-16 weeks is 37-85 mg/dL and triglycerides 20-114 mg/dL (Giknis and Clifford, 2008). The results of examining total cholesterol levels in the normal group were not much different from previous studies (Muntafiah, Yulianti, et al., 2017; Muntafiah, Ernawati, et al., 2017). Meanwhile, in the induced group (K2, K3, K4), total cholesterol levels were >110 mg/dL, and triglycerides were >170 mg/dL. The hyperlipidemia induction technique can increase total cholesterol and triglyceride levels higher than the previous study. It was three mL/200gBB/day of pork oil and two mL/200gBB/day duck egg yolk for ten days (Muntafiah, Ernawati, et al., 2017. Another one was giving pure cholesterol of 0.03 grams and 1 gram of pork oil for 28 days (Sambodo et al., 2019). All the administration has not propylthiouracil 12.5 mg/day, and a high-fat feed mixture of quail egg yolk and ducks egg yolk for 21 days (Untari and Pramukantoro, 2020). Pork oil contains about 38-43% saturated fatty acids and cholesterol. Pork oil continuously for 14 days resulted in increased cholesterol and triglyceride levels, accompanied by increased lipoproteins (hyperlipoproteinemia) in the blood. (Kusumastuty, 2014). Meanwhile, PTU can inhibit thyroid cells in experimental animals to inhibit thyroid hormone production and results in hyperthyroidism (Kurniati et al., 2018). This condition directly affects lipoprotein metabolism, increasing cholesterol levels (Untari and Pramukantoro, 2020). Propylthiouracil (PTU) is a thyroid hormone antagonist. Under normal circumstances, the thyroid hormone can increase fat metabolism. PTU is an antithyroid substance that can inhibit the formation of thyroid hormones that play a role in lipolysis so that inhibition of this thyroid increases blood cholesterol concentrations by expanding endogenous cholesterol biosynthesis (Diah et al., 2012; Kurniati et al., 2018).

Based on this study, at the end of the research period, a significant increase in total cholesterol and triglyceride levels occurred in K1 as a standard control. Various factors, including dietary factors, can cause this. In this study, experimental animal feed with AD II pellets, the fat content in it at least 4%, is thought to be one factor that causes an increase in total cholesterol and triglyceride levels. Meanwhile, in the K3 group, giving purple passion juice 4.2 mL/200gBB/day for 14 days can reduced total cholesterol and triglyceride levels (Table 1). Previous research by Soares et al. showed the same thing where P.edulis 1,000 mg/kg given twice a day for 28 days showed the effect of improving lipid profile by increasing HDL levels, lowering total cholesterol levels, and improving lipid peroxidation in Wistar's

Rat (Soares et al., 2012). Something different, in our study, purple passion juice can reduce triglyceride levels significantly.

What components are contained in purple passion juice so that they can reduce total cholesterol and triglyceride levels? Medical plant research generally carries out on unrefined plant extract materials that have various elements. It is said that the bioactive compounds contained therein can work together synergistically to produce an effect (Moreira et al., 2014; Briggs et al., 2014). Likewise, purple passion juice's antihyperlipidemic potency can be caused by various bioactive compounds contained in it. The essential nutrients needed by the body are found in this juice. This fruit juice contains much fibre, 2.81% protein, 6.57% carbohydrates, and <0.5% fat content. In 247 mL (1 cup) of juice contains 24% K, 60-80% Mg,> 80% P, and 90% Fe of the recommended dietary allowance of minerals. It has 1137 mg / 100 g of citric acid (Ramaiya et al., 2019). In addition to nutritional components, various literature through their research state that purple passion fruit contains multiple phytochemical compounds such as polyphenols, carotenoids, and vitamins (Matsui et al., 2010) insoluble fibre fraction which is beneficial for health. Purple passion fruit contains 1,060% flavonoids, 1.160% carotenoids, and 0.012% alkaloids. Flavonoids can lower total cholesterol levels in the blood (Matsui et al., 2010) (Kusumastuty, 2014) through the same mechanism as Simvastatin, a standardized and first-line drug in lowering cholesterol levels, by inhibiting the action of the enzyme 3-hydroxy 3-methyl glutaric coenzyme A reductase (HMG Co-A reductase) on cholesterol synthesis in the liver (McFarland et al., 2014). Besides, flavonoids can also reduce cholesterol absorption and increase cholesterol conversion into bile acids so that cholesterol levels in the blood decrease (Yunarto et al., 2019). Beta carotene can reduce cholesterol absorption in the intestines and increase the excretion of cholesterol through faeces. This situation causes the liver to make cholesterol in the blood converted into bile acids to reduce blood cholesterol (Silva et al., 2013). The content of vitamin C and fibre in purple passion fruit is also thought to play an active role in lowering blood cholesterol levels. Vitamin C works by influencing lipoprotein lipase activity and carnitine synthesis. Lipoprotein lipase (LPL) is an enzyme that plays a role in separating triglycerides from chylomicrons and VLDL. LPL catalyzes the breakdown of triglycerides into unesterified fatty acids and brings them to the adipose tissue for reprocessing and storage as triglycerides. Fibre content can reduce total cholesterol levels by inhibiting cholesterol reabsorption from bile salts in the intestine. This fibre will undergo fermentation in the intestine and then turn into short-chain fatty acids. It can increase the intestinal contents' viscosity so that the bile salts' cholesterol is excreted in the faeces (Matsui et al., 2010).

5 CONCLUSION

The provision of purple passion juice 4.2 mL/200gBB/day can improve the lipid profile of hyperlipidemia animals model by reducing total cholesterol and triglyceride levels. Simvastatin is more effective in lowering total cholesterol levels; however, purple passion juice is more effective in lowering triglyceride levels. The administration of purple passion juice and Simvastatin 0.18 mg/200gBB/day both had the same effectiveness in reducing total cholesterol levels in experimental animals.

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