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Antihypercholesterolemic Power of Red Dragon Fruit (*Hylocereus polyrhizus*) Peel Extract

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ABSTRACT

Background: The decoction of red dragon fruit peel contains chemical components with antioxidant activity of lowering blood LDL cholesterol levels. **Objective:** This research aimed to evaluate the antihypercholesterolemic power of red dragon fruit peel ethanolic extract. **Materials and Methods:** A total of 24 mice were divided into four treatment groups, each receiving distilled water at dose 0.39 ml/20 g body weight (A), red dragon fruit peel extract at dose 5.40 mg/20 g body weight (B) and 10.80 mg/20 g body weight (C), also simvastatin at dose 0.026 mg/20 g body weight (D). All experimental animals were given high fat intake in cow brain suspension for 60 days to increase LDL cholesterol levels in the blood. For 14 consecutive days, hypercholesterolemic mice were given test preparations. Mice were sacrificed on day 75 for blood and aortic samples. **Results:** The average blood LDL cholesterol levels in mice were 91.67 mg/dl, 63.23 mg/dl, 43.52 mg/dl, and 32.94 mg/dl ($p<0.05\%$). Meanwhile, the average aortic score was 1.09, 0.79, 0.76, and 0.91 in the groups A, B, C and D, respectively. **Conclusion:** Red dragon fruit peel extract at a dose of 5.4 mg/20 g and 10.8 mg/20 g body weight reduces blood LDL cholesterol levels and the risk of atherosclerosis.

Key words: Atherosclerosis, *Hylocereus polyrhizus*, LDL cholesterol levels, Red dragon fruit peel.

INTRODUCTION

In principle, the body needs cholesterol and triglycerides to make hormones, vitamin D, and bile acids that assist the intestines in the fat absorption process and a reserve energy source for the body.[1] However, fulfilling the need for inappropriate cholesterol and triglycerides as well as unhealthy lifestyles such as lack of physical activity or frequent consumption of foods with high cholesterol content have a terrible impact on health. This will lead to hypercholesterolemia or increased blood.[2-4] Hypercholesterolemia is suspected to be a factor in the development of coronary heart disease.[1,3,5] Furthermore, high LDL (low-density lipoprotein) cholesterol levels in patients can accelerate the occurrence of plaque which causes narrowing and hardening of the arteries.[3,4,6-8]

Atherosclerosis is a chronic condition characterized by the buildup of plaque in the arteries, which causes narrowing, hardness, and even total blockage.[6,8,9] Furthermore, it causes blood circulation to become not smooth. Obstruction of blood flow to the heart and brain can trigger heart attack and stroke.[7,10-12]

Adekiya *et al.* (2018)[3] stated that hypercholesterolemia is the total cholesterol concentration >240 mg/dl and LDL >160 mg/dl. According to Jempormase *et al.* (2016)[5] around 18% of the Indonesian population suffers from blood lipid abnormalities, with 80% dying abruptly from heart attacks and 50% showing no previous symptoms. Furthermore, efforts can be made to balance cholesterol levels in the blood and prevent atherosclerosis by limiting fat intake and ingesting antioxidant-rich preparations or foods.[13] Additionally, Andriani (2007)[14] stated that various antioxidants can slow the atherosclerosis process, including tocopherols, ascorbates, flavonoids, and lycopene (carotenoids). According to Tubagus *et al.* (2015)[15] the sunset musk mallow leaf extract includes flavonoid components that function as antioxidants and enhance serum lipids. In addition, modification of oxidized LDL increases the speed of metabolism, and the fiber content inhibits cholesterol absorption, hence, it can reduce cholesterol levels. Several other plant parts that can also lower blood cholesterol levels are *Anredera cordifolia* leaves,[2] *Peperomia pellucida* plant,[1] *Musa paradisiaca* fruit,[3] *Mikania micrantha* stem[4] and dragon fruit peel.[16]

Dragon fruit (*Hylocereus polyrhizus*) is widely cultivated and sold in West Kalimantan, Indonesia. It features a red peel and flesh, and the flesh is typically processed into food goods, beverages, or consumed straight, while the peel is underutilized. This is certainly bad because the dragon fruit peel includes a range of beneficial chemicals, including flavonoids and phenols, with antioxidant characteristics. Irmayanti & Ardiaria (2016)[16] state that red dragon fruit peel brew contains fiber, flavonoids and phenols. Furthermore, Noor *et al.* (2016)[17] stated that the extract contains vitamin C, flavonoids, tannins, alkaloids, steroids, and saponins. Red dragon fruit (*Hylocerus polyhizus*) peel brew at a dose of 800 mg/ml for 14 days effectively reduces LDL cholesterol levels in dyslipidemic mice.[16]

One technique to extract chemical compounds contained in a material is maceration. According to Husna *et al.* (2019)[18] maceration is a process of immersing materials using organic solvents at room temperature. It can effectively filter bioactive substances because the pressure difference between within and outside the cell causes a breakdown of cell walls and membranes, allowing secondary metabolites in the cytoplasm to dissolve in the solvent

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during the immersion phase. Furthermore, Truong *et al.* (2019)[19] stated that the type of solvent used is an essential parameter in isolating bioactive compounds from plants. According to Kurniawati *et al.* (2016)[20] 96% ethanol is a better solvent used in the maceration process than water because it produces more significant results and higher phenol content. This research evaluated the antihypercholesterolemic power of red dragon fruit peel ethanol extract.

MATERIALS AND METHODS

Extraction

After washing and separating the flesh and peel from 15 kg of fresh red dragon fruit, 5.83 kg was obtained. Furthermore, the peel was mashed using a blender and macerated using 96% distilled ethanol. Maceration was carried out for 3 x 24 hours and filtered every 24 hours. The filtrate was then separated, while the peel pulp was macerated by adding a new filter fluid. Finally, the entire filtrate was concentrated using a rotary evaporator at a temperature of 40°C, obtaining 30.31 g of the extract with a yield of 0.52%.

Experimental animals

The experimental animals used were 24 male mice of the Balb/c strain aged 2 months with a bodyweight of 24-30 g. They were obtained from the Central Laboratory of Food and Nutrition Studies, Gadjah Mada University, Yogyakarta, Indonesia. All experimental animals were adapted for seven days before the start of the trial. During the adaptation period, they were fed and watered ad libitum. The implementation of this research has been approved by the Health Research Ethics Commission of Dr. Moewardi Hospital, Solo, Indonesia, with Ethical Clearance No. 1.105/IX/HREC/2019.

Preparation of cow brain suspension

The preparation of cow brain suspension was consistent with Pratama and Probosari (2012).[21] Furthermore, 13 g of steamed and mashed cow brain was placed in a beaker and dissolved in 13 ml of distilled water. 0.13 g of cholic acid was then added and stirred until homogenous for 60 days.

Preparation of simvastatin solution

Kimia Farma's 10 mg simvastatin tablet was crushed and dissolved in 5 ml of distilled water in a mortar. The simvastatin was obtained by converting the dose in adult humans to mice. It was administered to mice at a dose of 0.026 mg/20 g body weight, the equivalent of 10 mg of human dosage.

Hypercholesterolemic mice model

Mice were induced by cow brain suspension at a dose of 0.28 ml/20 g body weight/day for 60 consecutive days.[21]

Testing the effects of red dragon fruit peel extract

All experimental animals were adapted for 7 days and randomly divided into 4 treatment groups consisting of 6 mice, respectively. Before blood sampling, all mice fasted for ±15 hours, and then blood was collected through the orbital sinus. Blood sampling was carried out on day 0 to determine the initial LDL cholesterol levels. After measuring the initial LDL cholesterol levels, from day 0 to 59 (for 60 consecutive days), all groups of mice were induced with cow brain suspension. Induction was carried out orally at a dose of 0.28 ml/20 g body weight/day. After receiving cow brain suspension for 60 days, on day 60, LDL cholesterol levels were measured. Hypercholesterolemia is diagnosed in mice with LDL values of 27 mg/dl, according to Kartikaningrum (2018).[22] In this experiment, induction was carried out to ensure that all experimental animals were in this condition. Furthermore, mice with blood LDL cholesterol levels of 27 mg/dl were given the test preparations once a day through oral administration for 14 consecutive days. The administration period of the test preparations was consistent with Faadlilah & Ardiaria (2016).[23] The first group was given 0.39 ml/20 g body weight of pure water suspension as a negative control. The second and third groups were given red dragon fruit peel extract at a dose of 5.40 mg/20 g and 10.80 mg/20 g body weight, respectively. Meanwhile, the fourth group as a positive control was given simvastatin at a dose of 0.026 mg/20 g body weight. Administration of test preparations started from day 61 to 74, and on day 75, mice blood samples were taken to measure LDL levels.

Measurement of LDL cholesterol levels

Blood samples were taken from the orbital sinus using a microhematocrit, then put into a 1.5 ml eppendorf tube. The samples obtained were centrifuged at 4000 rpm for 15 minutes. Meanwhile, about 10 µl of separated blood serum was taken using a micropipette and put into a test tube. For comparison, 10 µl of standard LDL precipitant (DiaSys) was added to the standard tube. In a test tube containing blood serum, 1000 µl of LDL precipitant (DiaSys) reagent was added using a micropipette, and then the samples were homogenized using a vortex. Finally, using a UV spectrophotometer at a wavelength of 500 nm, the absorbance of the samples was measured.

Data analysis

The data obtained were analyzed using SPPS version 24 for Windows. In addition, the average data for measuring blood LDL, cholesterol levels, and histopathological scores were analyzed using a one-way analysis of variance. Blood LDL cholesterol levels were further tested with a U-Mann Whitney level of 5%. In comparison, the histopathological score was further tested with Duncan level 5%.

Histopathological examination

The cervical dislocation was used to sacrifice animals, and the extracted aorta was routinely processed and stained with hematoxylin-eosin (HE). The histopathological staining was observed under an electric microscope.Histopathological scoring was determined based on the degree of damage in each visual field. It was scored 0 when there were no pathological changes, 1 when there was vacuolization in the vascular tissue, and 2 when there was vacuolization and thickening in the vascular tissue. In each slide, observations were made in 17 visual fields.

RESULTS AND DISCUSSION

Towil & Pramono (2014)[24] concluded from their findings that consuming cow brains can increase blood cholesterol levels. The increase is due to saturated fat and cholesterol content, where the digestion results produce free fatty acids, triglycerides, phospholipids, and cholesterol. These compounds are converted into chylomicrons after passing through the small intestinal mucosa. Furthermore, the rest of the breakdown of chylomicrons in free cholesterol with apoproteins forms VLDL (very low-density lipoprotein). Endothelial cell lipoprotein lipase enzyme then converts VLDL into IDL (intermediate density lipoprotein), which can last for 2-6 hours before turning into LDL.

The absence of receptors owing to genetic abnormalities such as familial hypercholesterolemia or saturated LDL receptors due to ingestion of high cholesterol foods causes atherosclerosis.[25] Increased LDL cholesterol levels in the blood cause disrupted cholesterol metabolism, resulting in a fat layer (fatty streak). This layer formed is initially thin and does not clog blood vessels. However, the thin, fat layer will gradually become fibrous plaque. Platelets adhere to the injured artery walls when the endothelial cells of the underlying

arteries are ripped apart for various reasons. The interaction between platelets and damaged endothelial cells stimulates connective tissue growth (proliferation) in the arterial wall called atherosclerotic plaque or atheroma. This atherosclerotic plaque grows progressively over the years to block blood flow.

This research was conducted to determine the hypercholesterolemic power of red dragon fruit peel extract in mice given cow brains. According to the findings, administering cow brain at a dose of 0.28 ml/20 g body weight/day can raise LDL cholesterol levels in all experimental animals. However, administration of red dragon fruit peel ethanol extract at doses of 5.40 mg/20 g and 10.80 mg/20 g body weight, as well as simvastatin at a dose of 0.026 mg/20 g body weight, results in a subsequent decrease in LDL cholesterol levels (Table 1).

Based on Table 1, the range of normal cholesterol levels in mice is in line with Kartikaningrum (2018),[22] which states that normal blood LDL levels range from 7 to 27 mg/dl. However, after giving a high-fat intake in cow brain suspension for 60 days, the blood LDL cholesterol levels increased to more than the standard limit. According to Kartikaningrum (2018),[22] mice can be categorized as suffering from hypercholesterolemia when LDL levels are 27 mg/dl. Furthermore, red dragon fruit peel ethanol extract reduced LDL cholesterol levels in mice, but not as much as simvastatin and distinct from distilled water, which did not decrease LDL cholesterol levels. This research investigated the histological description of the aortic blood arteries in mice to measure blood LDL cholesterol levels. Based on the degree of damage to the aortic vessels, the group with distilled water showed relatively severe changes. Meanwhile, the groups with red dragon fruit peel ethanol extract and simvastatin showed lower scores, which means the changes were relatively mild. These findings indicate that when mice were given simvastatin or dragon fruit peel ethanol extract for 14 days in a row, the reduction in LDL cholesterol levels did not reach the normal range. According to Rahmawati *et al.* (2016)[26] atherosclerosis was manifested above the normal limit for the duration of the experiment, even though LDL cholesterol levels have reduced.

This research showed a decrease in blood LDL cholesterol levels of mice in the treatment group with simvastatin and red dragon fruit peel extract. Simvastatin is a statin class drug that functions as a cholesterol-lowering drug and acts as a competitive inhibitor of HMG-CoA reductase (an enzyme that speeds up cholesterol synthesis). Statins inhibit the cholesterol synthesis step, namely converting 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) to mevalonate by the HMG-CoA reductase enzyme. Therefore, statin drugs have strong lipid-lowering potential that reduces the risk of cardiovascular disease. They also have anti-inflammatory, immunomodulatory and anti-thrombotic actions on the endothelium system. As with all medications, statins can cause musculoskeletal symptoms such as muscular pain (myalgia) or inflammation and an increased risk of diabetes and hemorrhagic stroke.[27,28]

The group with red dragon fruit peel extract at a dose of 10.8 mg/20 g body weight showed a higher reduction in cholesterol levels than at a dose of 5.4 mg/20 g body. Noor *et al.* (2016)[17] stated that red dragon fruit peel extract contains vitamin C, flavonoids, tannins, alkaloids, steroids, and saponins. It has antioxidant properties that can reduce blood LDL cholesterol levels. Li & Schellhorn (2007)[29] stated that vitamin C has the function of protecting against LDL oxidation by various types of oxidative stress and inhibiting LDL oxidation by vascular endothelial cells. According to Ardekani & Ardekani (2007)[30] vitamin C treatment for six weeks lowers LDL cholesterol levels and enhances blood lipid profiles. Pradana *et al.* (2016)[31] stated that flavonoids can inhibit the modification of LDL oxidation and reduce total cholesterol levels by lowering HMG-CoA reductase activity, Acyl-CoA acyltransferase (ACAT) activity and cholesterol absorption in the digestive tract. Pradana *et al.* (2016)[31] also stated that tannins are a class of compounds that can inhibit fat absorption in the intestine by reacting with mucosal proteins and intestinal epithelial cells, while alkaloids work as antioxidants by donating hydrogen ions. These compounds inhibit the activity of the pancreatic lipase enzyme to increase fat secretion through feces. As a result, the absorption of fat by the liver is inhibited since it cannot be converted into cholesterol.[32] Agustningsih *et al.* (2014)[33] stated that saponins reduce serum cholesterol activity. These chemicals decrease cholesterol by complexing with diet to prevent body absorption.

Red dragon fruit peel extract can protect blood vessels from damage caused by high cholesterol levels in the blood. This can be seen in Figure 2, where the condition of blood vessels in the extract group at a dose of 5.4 mg/20 g and 10.8 mg/20 g body weight seemed better than the distilled water group. The normal condition of blood vessels is due to the content of red dragon fruit peel extract, which has an antioxidant effect. Antioxidants can delay, slow down and prevent lipid oxidation. Specifically, antioxidants are substances that can delay or prevent the occurrence of oxidation reactions by free radicals in lipid oxidation.[34]

The content of vitamin C and flavonoids in red dragon fruit peel extract has an antioxidant effect that can prevent LDL oxidation. According to Hardjana *et al.* (2016)[34] supplementing mice with vitamin C can prevent increased endothelial cells of the tunica intima of arteries, a precursor to atherosclerosis. Vitamin C and the blood react with free radicals as oxidation products, causing LDL to be less atherogenic. The inhibition of LDL oxidation prevents the accumulation of cholesterol in the arterial walls, hence, there is no inflammation and proliferation of smooth muscle cells, which keeps it normal. Vitamin C, which has

Table 1: Showed that the average blood LDL cholesterol levels of mice given distilled water at a concentration of 0.39 ml/20 g body weight, dragon fruit peel ethanol extract at 5.40 mg/20 g body weight and 10.80 mg/20 g body weight, as well as simvastatin at 0.026 mg/20 g body weight. Day 0 describes the initial LDL levels of all experimental animals, while day 60 depicts the overall LDL levels by inducing hypercholesterolemia orally at a dose of 0.28 ml/20 g body weight/day. Finally, day 75 describes the LDL levels of hypercholesterolemic experimental animals given the test preparations for 14 consecutive days.

Group	Average LDL Levels (mg/dL)		
	Day 0	Day 60	Day 75
Distilled water (Negative Control) at a dose of 0.39 ml/20 g body weight	$23.79^{a} \pm 1.45$	$89.85^{a} \pm 1.45$	$91.67^{d} \pm 1.48$
Dragon Fruit Peel Ethanol Extract at a dose of 5.40 mg/20 g body weight	$24.02^{a} \pm 1.74$	$90.31^{a} \pm 1.74$	$63.23^{c} \pm 2.05$
Dragon Fruit Peel Ethanol Extract at a dose of 10.80 mg/20 g body weight	$23.34^{a} \pm 1.25$	$89.29^{a} \pm 1.25$	$43.52^{b} \pm 4.64$
Simvastatin (Positive Control) at a dose of 0.026 mg/20 g body weight	$22.67^{a} \pm 3.00$	$89.50^{a} \pm 3.00$	$32.94^{a} \pm 1.93$

Note: *) data are presented as mean ± SD (n=4), different letters in the same column indicate significant differences ($p<0.05$).

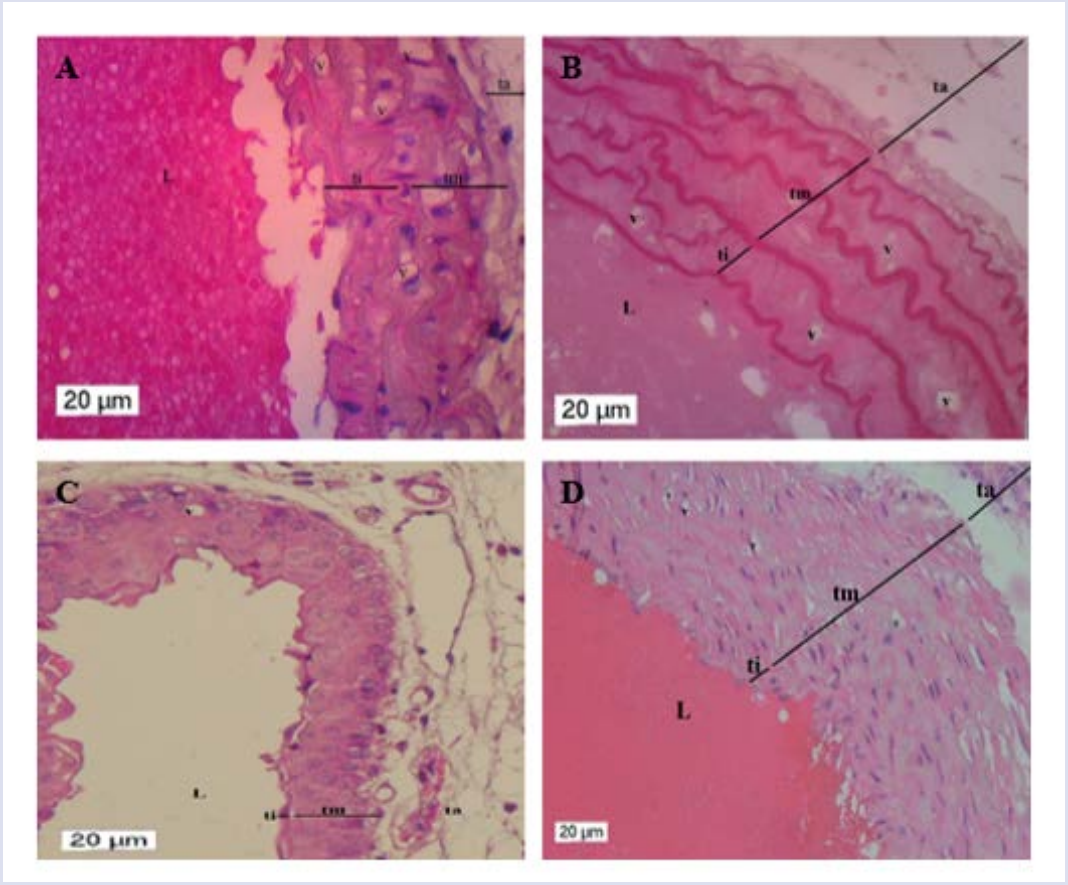

Figure 1: Histopathology of the aortic vessels in each treatment group. A. The group with distilled water at a dose of 0.39 ml/20 g body weight (negative control), B. The group with the dragon fruit peel extract at a dose of 5.40 mg/20 g body weight, C. The group with the dragon fruit peel extract at a dose of 10.80 mg/20 g body weight, and D. The group with simvastatin at a dose of 0.026 mg/20 g body weight (positive control). HE. 40x. bar= 20 µm. {(L= lumen) (ti= tunica intima) (tm= tunica media) (ta= tunica adventitia) (v= vacuolization)}.

Table 2: Showed the average score of aortic damage in hypercholesterolemic model mice after 14 days of administration of distilled water at 0.39 ml/20 g body weight, dragon fruit peel ethanol extract at 5.40 mg/20 g body weight, and 10.80 mg/20 g body weight, and simvastatin at 0.026 mg/20 g body weight.

Treatment Group	Average
Distilled water (Negative Control) at a dose of 0.39 ml/20 g body weight	1.09[b]
Dragon Fruit Peel Ethanol Extract at a dose of 5.40 mg/20 g body weight	0.79[a]
Dragon Fruit Peel Ethanol Extract at a dose of 10.80 mg/20 g body weight	0.76[a]
Simvastatin (Positive Control) at a dose of 0.026 mg/20 g body weight	0.91[ab]

antioxidant activity, also inhibits the oxidation of fatty compounds and prevents atherosclerosis. Nijveldt et al. (2001)[35] stated that flavonoids have antiatherogenic properties. These compounds have antioxidant activity that can inhibit LDL oxidation, hence, the integrity of the vascular endothelium is maintained and reduces the risk of atherosclerosis.

CONCLUSION

Red dragon fruit peel extract at a dose of 5.4 mg/20 g and 10.8 mg/20 g body weight can reduce blood LDL cholesterol levels and the risk of atherosclerosis.

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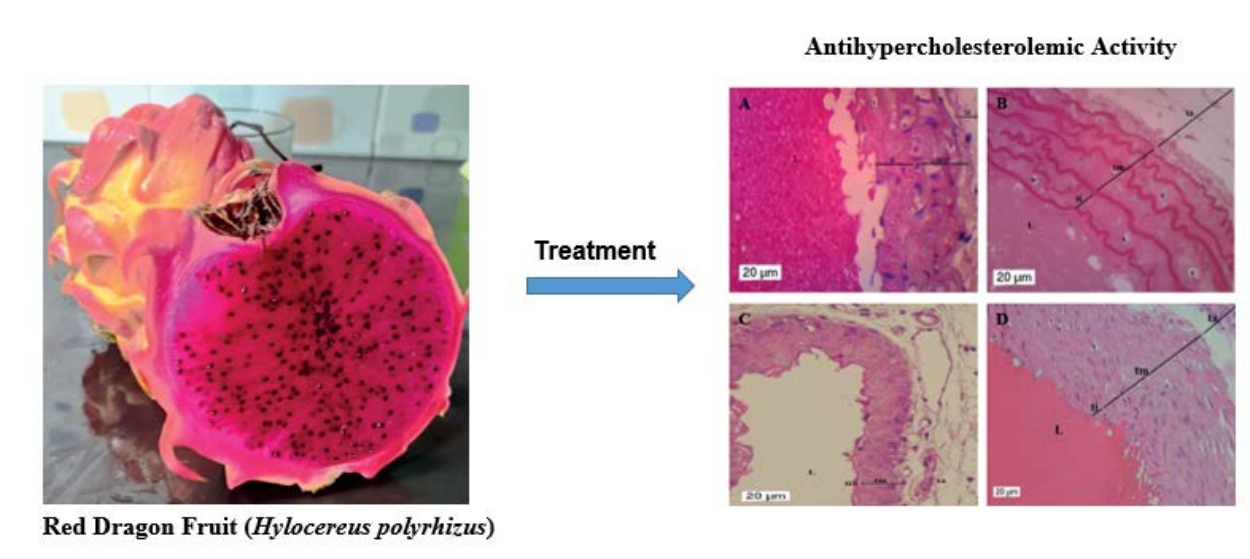
GRAPHICAL ABSTRACT



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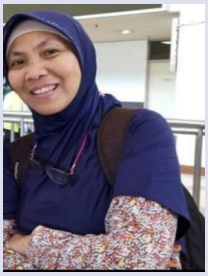

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