THE IMPACT OF DURIAN (DURIO SPP.) ADMINISTRATION ON THE BLOOD CHOLESTEROL LEVEL

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ABSTRAK

Menurut Riset Kesehatan Dasar (Riskesdas) 2007 Indonesia menunjukkan bahwa penyakit tidak menular (PTM) adalah penyebab utama kematian di Indonesia. Penyakit Kardiovaskuler menjadi penyebab utama dengan 31,9% termasuk hipertensi (6,8%) dan stroke (15,4%).[1] Risiko penyakit meliputi makanan. Salah satu makanan yang dipercaya mempunyai hubungan dengan penyakit jantung dan strok adalah durian. Durian (*Durio spp.)* adalah salah satu buah tropis yang disenangi di regio Asia Tenggara, termasuk Indonesia. Berita yang beredar dimasyarakat menyatakan bahwa konsumsi durian dalam jumlah besar pada waktu relatif singkat dapat menyebabkan yang efek tidak baik untuk kesehatan. Maka, penelitian ini bertujuan untuk membuktikan apakah konsumsi durian dalam jumlah yang besar dalam waktu yang relatif singkat berpengaruh terhadap kadar kolesterol plasma tikus.

Dalam percobaan ini setiap grup yang terdiri dari grup kontrol maupun intervensi terdiri atas enam ekor tikus. Grup pertama mengkonsumsi durian selama satu minggu, grup kedua diberi intervensi durian selama dua minggu dan grup ketiga diberi intervensi durian selama tiga minggu. Durian yang diberikan dilarutkan dalam air dengan dosis yang sama dengan konsumsi lima buah durian/manusia/hari. Tikus lalu dikorbankan diakhir percobaan dan darahnya diambil untuk mengukur level dari kolesterol menggunakan kit (ST. Reagensia, Indonesia). Riset ini dilakukan dalam periode Juli 2012 sampai April 2013.

Pada minggu pertama, level kolesterol dari enam tikus yang hidup adalah 68,617 $\pm$ 21,676 mg/dL. Pada minggu kedua experimen, level kolesterol darah dari grup kedua yang terdiri dari tiga ekor adalah 58,534 $\pm$ 7,528 mg/dL dan grup perlakuan tiga minggu memiliki nilai kolesterol 55,654 $\pm$ 0,489 mg/dL dengan nilai kolesterol darah dari kontrol keseluruhan sebesar 75,497 $\pm$ 15,486 mg/dL

Dari percobaan ini, dapat dilihat bahwa terjadi penurunan nilai kolesterol darah. Namun, secara statistik tidak ditemukan perbedaan bermakna ($p>0,5$). Dapat dilihat bahwa kolesterol tidak meningkatkan level kolesterol darah.

Dari survei literatur, ditemukan bahwa durian tidak mengandung substansi yang berbahaya. Di sisi lain, hasil percobaan menunjukkan tidak ada peningkatan level kolesterol darah bahkan sebaliknya. Studi literature menyatakan bahwa durian mengandung substansi antioxidan yang secara tidak langsung dapat mengurangi level kolesterol darah. *Kata kunci: kolesterol, kolesterol darah, durian.*

ABSTRACT

Since long time, Durian (*Durio spp.*) is appreciated and consumed widely in Southeast Asia countries. However, there is a rumor among people that

consuming durian in a relatively great number and in relatively short time could cause dangerous effect such as increase in the blood cholesterol level, heart attack, abortion, or even stroke. Therefore, the aim of this investigation is to test whether the durian consumption in relatively long time could increase the blood cholesterol level.

A number of rats were divided randomly into a group of 6 animals. The first group was fed with durian for 1 week, second group for 2 weeks, and the third group for 3 weeks. The durians were dissolved in water in a dose equivalent to five-durians/ human/day. The rats were sacrificed at the end of each period and blood was collected for cholesterol level, which is determined using a special kit (ST. Reagensia, Indonesia). The research was conducted from July 2012 to April 2013.

At the first week, the blood cholesterol level of 6 survival rat was 68,617 $\pm$ 21,676 mg/dL. After 2 weeks of experiment, the blood cholesterol level of the second group 3 of 9 was 58,534 $\pm$ 7,528 mg/dL. Later on, in 3 weeks intervention the blood cholesterol level (3 rats) was 55,654 $\pm$ 0,489 mg/dL. Compare to blood cholesterol level in control group (5 rats), which was 75,497$\pm$ 15,486 mg/dL

In conclusion, it seems that there were a decrease in blood cholesterol level in durian fed rats. However, statistical analysis shows that the different is not significant. It appears that the durian consumption did not increase blood cholesterol level.

From literature survey it is found that durian does not contain any harmful substance. Instead of increasing blood cholesterol level, durian contains antioxidant substance, which indirectly can reduce the blood cholesterol level.
Keywords: cholesterol, blood cholesterol, durian.

1. Background

The prevalence of non-communicable diseases is increasing in time. One of the diseases that have high prevalence is cardiovascular disease. It is predicted that in 2030 there will be about 23,6 million people will die because of cardiovascular disease.[1] Several methods are conducted to control increasing number of this disease. One of the ways is by intervention to the modifiable risk factors including diet. Diet that is well known to be one of the contributors for cardiovascular disease is durian.

Durian grows in tropical Asia countries, such as Indonesia, Malaysia and Brunei Darusalam. This fruit is consumed by the society without considerting the nutrient values. Durian has a special position in the society and called as “king of fruits.”[2] The size of this pale green to brown color fruit varies from 25-30 cm long and 15 cm in diameter with the weight from 1 to 3 kg.[3]

In the society there are several stories in regard to the side effects of durian. For example if durian is consumed in inappopriate amount it may cause an

increament in cholesterol level in the blood and misscarriage in preganant mother. The rise in blood cholesterol level is correlated with the formation of atherosclerosis and leads to cardiovascular disease. However, there is no research proving the effect of durian to the blood cholesterol level.

The purpose of this experiment is to prove the existence of rise level in blood cholesterol after the exposure of large amount of durian consumption. In regard to know the answer, we purpose to conduct a research on rat fed with excessive amount of durian and observe the effect of this treatment on blood cholesterol level.

2. Literature Review

2.1. Cardiovascular Disease

2.1.1 Epidemiology

The trend of having infectious disease has shift to the trend of non-communicable disease, including the cardiovascular and diabetes. Ischemic stroke and atherosclerosis is now the new global problem since they are the leading causes of death and disability. The number continues to rise on account of fact that preventive programs are still ineffective. In 2008, there were 17,8 million death and 7,3 million of them is caused by heart attack and 6,2 million for stroke.[5] In Indonesia, basic health research, 2007 (Riskesdas) reported that cardiovascular disease (31,9%), hypertension (6,8%), and stroke (15,4%) were the major causes of mortality.[6]

2.1.2 Etiology and Risk Factors

2.1.2.1 Etiology

There are two types of cardiovascular disease etiology, which are:[4, 7]

1. Common etiology
    - Thrombosis
        - Lacunar stroke
        - Large vessel thrombosis
        - Dehydration
    - Embolic occlusion
        - Artery to artery

- Cardioembolic

2. Uncommon
   - Hypercoagulable disorders
   - Venous sinous thrombosis
   - Fibromuscular dysplasia
   - Vasculitis
   - Cardiogenic
   - Subarachnoid hemorrhage vasospasm
   - Drugs
   - Eclampsia

2.1.2.2 Risk Factors

There are several risk factors that can be related to cardiovascular disease, as following:[4, 8]

1. Modifiable factors
   - Hypertension (high blood pressure)
   - Tobacco use
   - Raised blood glucose (diabetes)
   - Physical inactivity
   - Unhealthy diet
   - Cholesterol/lipids
   - Overweight and obesity
2. Non-modifiable factors
   - Age
   - Gender
   - Family History

2.1.2.3 Pathophysiology of Atherosclerosis

Atherosclerosis is an inflammatory process of the endothelial vessel wall, which occurs in the cardiovascular system.[4, 6] Atherosclerosis occurs when there is an excessive LDL cholesterol and intensifying factors such as free radicals in blood vessel layer. Firstly, the LDL transports cholesterol to the peripheral blood

vessels. The endothelial wall will become permeable to lymphocyte and monocyte and leads to inflammation. The formation of atherosclerosis does not appear in a short moment of process. It occurs begin in childhood and account for 20-30 years process. Lifestyle and other comorbid disease such as diabetes play a big role in the initiation of atherosclerosis.

In the process of cholesterol transport, the cholesterol that is brought by LDL to the peripheral blood the monocyte will engulf the unwanted substance that exist. However, in excessive amount of cholesterol, the monocyte will transform into macrophage so called as foam cells. The exogenous cholesterol will repress the expression of LDL-receptor, which in this case LDL receptor will be lessen in the condition of uncontrolled cholesterol. The ingestion of lipids will help the mononuclear phagocytes may remove the occurring lipid. However, lipid accumulation will form atheroma if there is no balance between eradicated and impeding lipid. [6]

Some lipid from the intimal lesion will be banished as the intimal lesion grows, and similar condition take place to foam cells as the result of apoptosis program. The death of mononuclear cell will accumulate and become atherosclerotic plaque.

Continuing the process, monocyte will later produce cytokines and growth factors that further produce exaggerating effect, which may complicate the occurring plaque, which may build-up fibrous tissue formed by extracellular matrix. The smooth-muscle cell synthesizes the bulk of extracellular matrix complex atherosclerotic lesion, which arrives from tunica media. The arrival of smooth-muscle and extracellular matrix will amplify the existence of foam cells. When the process continuously happens, it will thinner the wall of tunica intima and accompanied by fissuring endothelial wall, which may rupture. [4, 6]

When the plaque rupture, the lipid fragments and cellular debris will enter the vessel lumen and will be exposed to thrombogenic agents on the endothelial

surface. The process will result a thrombus formation and possible to block a coronary or cerebral blood vessel that results in a heart attack or stroke. [4, 6]

2.2 Durian

2.2.1 Definition

Durian (Durio zibenthinus) is a plant species that have a strong penetrating odor with thorn-formed cover, which have greenish to yellowish pale for the fruit. It belongs to Bombacaceae family and genus of Durio and called as the "king of fruits," which have the properties of dicotyledonous and grows seasonally. Durian is harvest from trees that the approximately 25-50 m in height and thrive well in tropical countries with the temperature between 25 and 30°C.[9]

2.2.2 Nutrition facts

As part of exotic group fruits, Durian is recently known for its antioxidant and anti-proliferative effects observed from its bioactive and nutrient compounds.[8] Durian is proven has the composition of polyphenol, flavaoid and flavanols and in some experiments the properties was count using Beta-carotene and 1,1-diphenyl-2-picryl- hydrazyl radical (DPPH) at different stages of ripening.[8,10] It was found that polyphenol and antioxidant activity were highest in overripe, flavonoid in ripe, flavanols and antiproliferative in mature durian.[9] The bioactivity is highly related with ripe condition and the polyphenols were the highest contributor for the antioxidant capacity of durian.[11] An among some culvators of durian, Mon-thong is the type that has the highest anti-oxidant activity [12]

Table 1.Durian fats component[13]

Fats and Fatty Acids		
Amounts Per Selected serving		% DV
Total Fat	13.0 g	20%
Saturated Fat	~	~
Monounsaturated Fat	~	
Polyunsaturated Fat	~	
Total trans fatty acids	~	
Total trans-monoenoic fatty acids	~	
Total trans-polyenoic fatty acids	~	
Total Omega-3 fatty acids	~	
Total Omega-6 fatty acids	~	

Table 2. Durian Nutrition Facts[13]

Nutrition Facts	
Amount per serving (in 243 g)	
Calories 357	
	% Daily Value
Total Fat 13g	20%
Saturated Fat	0%
Trans Fat	
Cholesterol 0 mg	0%
Sodium 5mg	0%
Total Carbohydrate 66g	22%
Dietary Fiber 9g	37%
Sugars	
Protein 4g	

On the other hand, compared to other tropical fruit such as papaya and pineapple, durian has the lowest glycaemic index,[10] and highest antioxidant capacity among mangosteen and snake fruit[14]. Interventional research using durian suggests there is no toxin effect indicated after giving durian and there is also no weight gain difference. The hematologic result and clinical data of glucose, creatinine, and BUM in treated groups was found normal. The mean value of cholesterol was rather low compared to control group.[15] A decrease antioxidant capacity happened in rat given by cholesterol, which indicates that durian has the activity to lower the cholesterol level. [9]

2.3. Cholesterol

2.3.1 Definition of Cholesterol

Cholesterol is an amphiphatic lipid that can easily dissolve in cell. There is another kind of cholesterol with the addition of long chain fatty acid. They are transported through out the body by lipoprotein. The precursor of cholesterol is the acetyl-Coa. Cholesterol is the substance for hormones production such as corticosteroid hormones, bile acid, vitamin D, etc. The source of cholesterol is from daily diet and production by the body in inadequate amount.[16]

Cholesterol is absorbed through the intestinal lumen by diffision-controlled process. Enterocyte also control the condition of unwanted or excessive amount of cholesterol with the same process. There is a gene, which codes adenosine triphosphate (ATP)-binding cassette (ABC) protein family that has a role in the sterol transportation. The role is to remove the unwanted or excessive cholesterol and plant sterol (phytosterols) that located in the enterocyte to the gut lumen. The defect on these genes will lead to excessive amount of cholesterol on the bloodstream and result in increasing prevalence of cardiovascular problem.[17]

Cholesterol is basically a modification of sterol compound, which includes the perhydrocyclopentanophenanthrene with four fused rings. In the plasma, one third of the cholesterol is in the free from, while two third other is in long chain-fatty acid (usually linoleic acid). It is attached at hydroxyl C-3 group A ring. [16, 17]

2.3.2 Cholesterol Synthesis

The formation of 27 carbon rings cholesterol through out different multimolecular interaction results from acetyl-CoA. Acetyl-CoA can be acquired from severel process for instance beta oxidation of fatty acids, the ketogenic amino acids, and pyruvate dehydrogenase reactions. Some carbons are obtained from methyl group of acetyl-CoA but some others are from carboxylate atom of acetyl-CoA.[18] In our body, cholesterol is made in the cytosol of the cell that requires hydrolysis of high-energy thioester bonds of acetyl-CoA and phosphoanhydride bonds of ATP. It happened in four stages, which are:[15, 16]

1. Synthesis of Acetyl-CoA from Mevalonate

The synthesis will take place on the cytoplasm. At first the acetyl-CoA will be condenced together to form acetoacetyl-CoA. The process is catalyzed by cytosolic thiolase enzyme. The condensation of acetoacetyl-CoA the is helped by HMG-CoA synthase to generate HMG-CoA. This HMG-CoA further will be reduced by NADPH catalyzed with the helped of HMG-CoA reductase to form mevalonate.

2. Isoprenoid formation

In the cholesterol synthesis, the mevalonate from previous reaction will by phosphorylated by ATP after decarboxylation process to be active isoprenoid unit, isopentenyl disphosphate.

3. Squalene formation from six isoprenoid

The isopenthyl diphosphate is formed by a shift of double bond to form dimethylallyl diphosphate then condensed with other isopenthyl diphosphate to form ten-carbon intermediate geranyl diphosphate. The process continues with other condensation of isopentenyl diphosphate to form farnesyl diphophate. After the sequence, the condensation proceed between farnesyl diphosphate to form squalene. The inorganic pyrophosphate then eliminated forming presqualene diphosphate and reduced by NADPH with the elimination of inorganic pyrophophate molecule.

4. Lanosteron formation

The folding of squalene will appear similar to steroid molecue. Before the ring closure, the squalene will be converted to squalene 2,3-epoxide by the help of function oxidase in the endoplasmic reticulum in squalene epoxidase. The methyl group of C14 will be given to C_{13} and catalyzed by oxidosqualene named lanosterol cyclase.

5. Formation of Cholesterol

The cholesterol formation started with the lanosterol takes place in the endoplasmic reticulum. The changes occurs in the steroid nucleus. The methyl groups on C_{14} and C_4 are removed to form 14-desmethyl lanosterol and then zymosterol. The double bond C8–C9 and will form desmosterol. The double bond of the side chain is then lessen to produce cholesterol.

2.3.3 Cholesterol Metabolism

Cholesterol metabolism cannot be separated with the lipid metabolism. Lipid is substance that consists of triacylglycerol, cholesterol, and phospolipid. One can obtain lipid from it dietary intake or synthesis by its own body. Lipid in the body is transported by protein with the property lipid and protein called as lipoprotein. The lipid metabolism is strongly correlated with the presence of this protein.

Lipoprotein is separated into some different types by it composition of lipid. There are chylomicron, very low density lipoprotein, low-density lipoprotein and high-density lipoprotein. These lipoproteins will help the metabolism process as below:

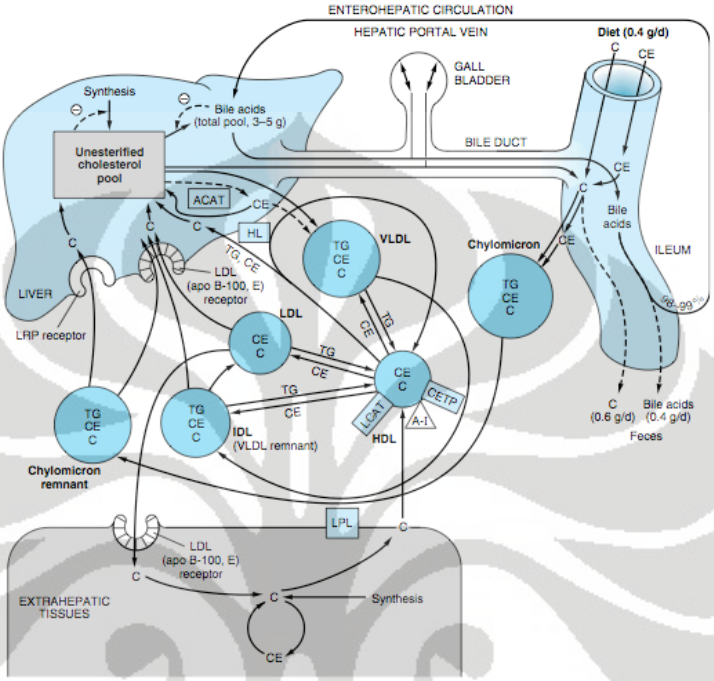

Figure 1. Transport of cholesterol in human body[16]

Firstly, the body obtains exogenous fat from the dietary intake. It is known as the exogenous pathway when the fat is then surrounded by the cylomicron. The fat that enter the intestine is then broken down and will be surrounded by lipoprotein to form nascent chylomicron. This nascent chylomicron contains triacylgliceride (TAG), Apo-B48, Apo-A, cholesterol and phospolipid. In the form of chylomicron, it will be absorbed and enter the blood stream. The blood has many properties including HDL. The HDL that has Apo-C II and Apo-E that will interact with the cylomicron. The Apo CII has the properties to activate the lipoprotein lipase (LPL) enzymes that have the function to degrade triacylglyceride to be glycerol and fatty acid that is in the chylomicron.

Moreover, the glycerol that is obtained from triacylglyceride breakdown will undergo the chemical reaction to be glycerol 3-phosphate. Glycerol also being

used to resynthesis triacylgliceride in the liver. On the other hand, fatty acid from the triacylgliceride will be stored as triacylgliceride in adipose and breast tissue or as energy source in the heart or skeletal muscle.

Recalling the nascent chylomicron that interact with HDL and undergo reaction with LPL. The nascent chylomicron without the existence of TAG, the term will be chylomicron remnants. Moreover, the remnants of chylomicron will be absorbed by the liver helped by Apo-E though mediated endocytosis.

The process continues with the production of very low-density liporprotein (VLDL) as it is constitute from previous chylomicron with addition from cholesterol and phospolipid from previous chylomicron. VLDL contains triacylgliceride and other constituents such as cholesterol, phopolipid, Apo B-100, and Apo-C.

VLDL will travel to the entire body through bloodstream. It will become the mature VLDL. Similar to chylomicron, the TAG of VLDL will be degraded by LPL of the HDL resulting loss of TAG.

The absence of TAG will change the VLDL to be VLDL remnants, which half of the remnats will enter the liver by the help of Apo-E receptor through endocytosis process. The other 50% will form Intermediate Density Lipoprotein (IDL) that is made of cholesterol, Apo-B 100, and Apo-E, which then also enters the liver.

Continuing the process, the Low Density Lipoprotein (LDL) will be formed after IDL. The LDL is composed by cholesterol and cholesterol esters. The 60% of LDL will enter the liver by the help of Apo-B 100. The remaining number of LDL will travel to adrenal gonad, gonad and skin to be the source of steroid hormones, vitamin D, and membrane structure. When the LDL is excessive in number, it will travels through the blood stream. It will lead to saturated of the receptor. The LDL will be captured by macrophage and if the position is near the endothelial cell, it will induce inflammatory cytokines.

The other type of lipoproteins is High Density Lipoprotein (HDL), which the process is rather different from other lipoproteins. It is formed in liver and the intestine, and has several main functions such as transports the excess cholesterol from the peripheral to the liver. The other function is to exchange proteins and lipids between chylomicron and VLDL. HDL has the function to transfer cholesterol esters to another lipoprotein mediated by cholesteryl ester transport protein (CETP). After entering the liver, free cholesterol and cholesterolester from HDL will be endocytositosized and degraded in lysosome.

Related to the process in lipoprotein above, the exchange between lipoprotein and HDL will transform nascent HDL into mature HDL. Mature HDL can bind to specific receptors in the liver and scavenger receptor SR-B1 in different cell types. The main function of HDL itself is for reverse cholesterol transport, which then the cholesterol secreted, from the liver as bile salts or repackaged as VLDL.

3. Research Methods

Variables to be measured

- The duration of durian consumption as the independent variable.
- Blood cholesterol level as the dependent variable.

Methods

A. Rat Preparation

a. The rats was divided into four distinct groups:

1. The group of the rats that do not consume durian
2. The rats that consume durian for 1 week
3. The rats that consume durian for 2 weeks
4. The rats that consume durian for 3 weeks.

b. Group 2,3 and 4 beside being fed by standard diet, it received an excessive amount of soften durian once daily for 1 week (group 2), 2 weeks (group 3) and 3 weeks (group 4). All rats receive normal diet and ad libitum daily.

c. At the end of specific group periods, each rat was sacrificed in deep ether anasthesia.

d. Blood of each rats was taken directly by heart punctre and collected in heparinized tube.

e. The blood through centrifugation, was separated to be plasma at 3000 rpm for 15 minutes. Plasma is later going to be used to measure cholesterol level. Plasma was essayed using a special kit (ST. Reagensia, Indonesia, AKD 10101400087)

Data Collection

a. Each rat was given a mark for a purpose of easier rat identification.
b. The rat weight was calculated at the beginning and immediately before the sacrifaction.
c. Rats were sacrificied in different time according the intervention time. Group two was sacrificied one week after intervention, group three was sacrificied two weeks after intervention and group four was sacrificied three weeks after intervention.

Durian Preparation

a. The fruit was purchased grom the near local market.

b. Durian was separated from its cover and peeled off to obtain the pulp.

c. The pulp was diluted in water.

d. The durian was administered to each experimental rats by esophageal tube two times/day with 2 ml durian/ administration.

Data Analysis

Data analysis was conducted to know the distribution of data between dependant and independent variable using univariat analysis, while the bivariat analysis was used to know the relation between dependant and independent variable. If the data is not normaly distributed, then it should be changed to logarithmic form.

Analysis that is used to know the relationship between duration of durian intervention and cholesterol level is Mann-Whitney because the distribution of data is abnormal. Spearman's rank correlation coefficient or Spearman's rho is used in nonparametric measurement if there are two variables that statistically dependence. In this case, Spearman's rank correlation is used to see the correlation between duration of durian consumption and blood cholesterol level.

4. Result

The experiment was conducted in Faculty of Medicine Universitas Indonesia using 27 rats. However, during the experiment some of the rats died. The cause of the death varied, for example unable to control the stress, eaten by other rat, and other unknown cause.

The measurement of the blood cholesterol used an equation to get the blood cholesterol level that is ascribed in the appendix.

1. Cholesterol Level

Table 3. Blood Cholesterol Level (mg/dL) for each group

No	Control	Group 1 (1 week intervention)	Group 2 (2 weeks intervention)	Group 3 (3 weeks intervention)
1	59.802	89.185	60.839	55.308
2	69.827	80.197	50.123	56
3	66.716	40.098	64.641	Died
4	99.21	63.259	Died	Died
5	81.93	47.703	Died	Died
6	Died	91.26	Died	Died
Mean	**75.497**	**68.617**	**58.534**	**55.654**
SD	**15.486**	**21.676**	**7.528**	**0.489**
		Statistical Analysis		**0,302**
		Correlation		**0,027**

The average amount of blood cholesterol level can be seen in table. 3. It shows the blood cholesterol level for each group after durian intervention related to time.

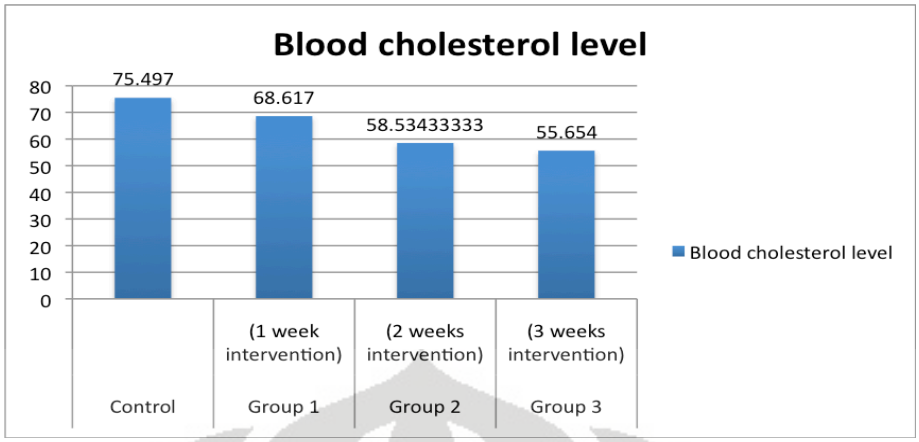

Figure 2. Blood cholesterol level diagram (mg/dL)

From figure.2. it can be seen that there is an decline in mean blood cholesterol level in interventional group (group 1, group 2 and group 3) compared to the control group and time intervention. The control group shows the mean blood cholesterol level of 5 rats is 75,497± 15,486 mg/dL. On the other hand, the first intervention group present 68,617 ± 21,676 mg/dL of blood cholesterol, while the second group shows a downtrend of blood cholesterol with blood cholesterol level mean 58,534 + 7,528 mg/dL. The third group also shows a decrease in blood cholesterol level with 55,654 ± 0,489 mg/dL.

5. Conclusion

1. There is a decrease in blood cholesterol level of interventional groups in comparison to control group.
2. Durian has a negative correlation with plasma cholesterol level, which it decrease the total cholesterol level.
3. The decline of total cholesterol level does not directly mean that durian is safe to be consumed in large amount. Dyslipidemia can occur from other aspect such as trigliceride that needs to be observed in further research.

It is recommended for the future research project to administer durian gradually as the gaster volume the rat was small.

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