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Research

Ethyl Acetate and Butanol Fraction Effect of *Citrus Japonica* Thunb. On Triglyceride Levels In Serum White Male Rats *(Rattus Norvegicus)*

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ABSTRACT:

Hypertriglyceridemia is condition when there is an increase of triglyceride levels in blood. Hypertriglyceridemia can be increased blood pressure and heart problems. One of the plants can be used as a medicine is kasturi citrus peel (*Citrus japonica* Thunb.). This study aimed to determine the effect of giving butano fraction and ethyl acetate fraction of kasturi citrus peel (*Citrus japonica* Thunb.) to triglyceride levels on male white rats (*Rattus norvegicus*). The parameters are triglyceride levels in serum of male white rat induced with high-fat feed containing quail egg yolk (10 ml/kgWB). This research used 25 male white rats that divided into 5 groups with 5 rats per group. Normal groups are not given any treatment, only standard feed. The negative group was induced by high-fat feed and suspension Na CMC, the positive group was given high-fat feed and atorvastatin suspension 0,9 mg/kgWB and treatment group was given high-fat feed induction and suspension of ethyl acetate and butanol fraction of kasturi citrus peel with doses 250 mg/kgBW, as much 1% of body weight wich given orally. The triglyceride levels are calculating by using colorimetri enzymatic method with a photometer Mindray® (BA-88A) at wavelength 510 nm. The data percentage change in triglyceride levels on day 29 to day 15 obtained were analyzed with one-way *Analysis of Variance* (ANOVA) and continued with the *Post Hoc Tukey* test for each fraction. The results showed that giving butanol fraction and ethyl acetate fraction of kasturi citrus peel (*Citrus japonica* Thunb.) at doses of 250 mg/kg body weight had an effect on the decrease in triglyceride levels in serum of white male rat indicated by a significant difference ($p<0.05$) with negative control and showed a decrease in triglyceride levels activity that was not significant difference ($p>0.05$) with atorvastatin and there is no significant difference between anti hypertriglyceride activity of butanol fraction and ethyl acetate fraction ($p>0.05$)

KEYWORDS: Butanol Fraction, Ethyl Acetate Fraction, Kasturi Citrus Peel (*Citrus japonica* Thunb.), Triglyceride, White Male Rat.

INTRODUCTION:

One of the lipid components in blood plasma, namely triglycerides. Triglycerides are energy reserves stored in adipose and muscle tissue. If the body needs energy, then triglycerides are released to be metabolized into energy . High amounts of triglycerides (hypertriglyceridemia) are a risk factor for cardiovascular disease[1]. Based on the 2018 Basic Health Research (Riskesdas), it states that the percentage of incidents of 2018 Indonesian residents aged ≥ 15 years who have high triglyceride levels is 13.3%. Meanwhile, based on the gender category, men have higher triglyceride levels, which is 16.3% compared to women, only 11.4%[2].

High triglyceride levels in the blood will increase the concentration of very low density lipoprotein (VLDL) which then increases the risk of plaque deposits forming in the arteries, increasing blood pressure and heart problems. Decreasing triglyceride levels will reduce the risk of heart problems and atherosclerosis[3]. Decreasing levels of triglycerides in the blood can be done in various ways, namely by taking drugs and changing lifestyle. The use of synthetic drugs has been shown to be effective at reducing lipid levels, but these drugs have side effects such as indigestion, myopathy and redness of the skin [4].

Indonesia has a variety of plants that have the potential to act as medicines for the community, one of which is the kassuri citrus plant (Citrus japonica Thunb.). Based on the results of examination by Bhat et al, (2011)[5], the bioactive components of citrus citrus (Citrus japonica Thunb.) Include ascorbic acid of 40.20 ± 0.5 mg / 100 mL, total phenolic 336.0 ± 1.3 mg / 100 mL , total flavonoids 0.37 ± 0.1 mg / 100 mL, and total flavonols 1.41 ± 1.2 mg / 100 mL. In addition, the skin of the citrus fruit contains flavonoids consisting of flavonoids (naringin, hesperidin and neohesperidin), flavones (diosmin, luteolin and sinensetin), flavonols (routine, quercetin, kaemferol) and phenolic acids [6].

Kurowska et al, (2000) found that flavonoid compounds from citrus fruits such as hesperidin and naringin can reduce LDL cholesterol and triglycerides and can increase HDL cholesterol in hypercholesterolemic individuals[7]. Surlitah et al, (2017) explained that there was a decrease in plasma triglyceride (TG) levels, plasma Low Density Lipoprotein (LDL-c), plasma total cholesterol (TC) and an increase in High Density Lipoprotein (HDL-c) plasma of adult women who are overweight after consuming musk orange juice[8]. The results of research by Sandriyana (2018) showed that the ethanol extract of the skin of the citrus fruit at doses of 500 and 1000 mg / kg body weight had an effect on reducing triglyceride levels as indicated by a significant difference ($p < 0.05$) with negative control $p = 0.000$, while the dose 250 mg / kgBW had no effect on decreasing triglyceride levels as indicated by no significant difference ($p > 0.05$) with negative control $p = 0.995$[9].

In this study, male rats were tested because they have a more stable biological body condition than female rats which will be affected by the presence of the estrous cycle and pregnancy[10]. The solvent used in this research is ethyl acetate which can dissolve semi-polar compounds. One of the compounds present in the ethyl acetate fraction are flavonoids. The comparison used in this study was atorvastatin. Atorvastatin is a statin drug that has a long half-life [4]. Atorvastatin inhibits cholesterol synthesis by inhibiting the HMG-CoA reductase enzyme, causing an increase in LDL receptors in the liver. This LDL receptor can bind to apoB 100 (VLDL), HDL-C, LDL and chylomicrons. VLDL and chylomicrons are lipoproteins from triglycerides, if this happens it can lower triglyceride levels 11. Based on the description above, the authors are interested in examining the effect of giving the ethyl acetate amd butanol fraction of the kasturi citrus peel on reducing triglyceride levels in male rats.

MATERIAL AND METHODS:

Research Tools

The tools for making the extract are in the form of a distillation device, vacuum rotary evaporator (Buchi®), filter paper, aluminum foil, dark bottle, funnel, beaker (Pyrex Iwaki®), desiccator. The tools for phytochemical testing are spatula, mortar and stamfer, drop plate, test tube (Pyrex Iwaki®), dropper pipette, spirit lamp. Tools for activity testing are analytical scales (Shimadzu Auw 220®), animal scales, watch glasses, spatels, measuring cups (Pyrex Iwaki®), oral syringes, microhematocrit pipettes (Marienfeld®), centrifuges, centrifuge tubes, micro pipettes, tips, tubes eppendrof, and a set of measuring tools for triglyceride levels (Photometer Mindray BA-88A®).

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Research Materials :

The ingredients used to make extracts and fractions are the peels of the kasturi citrus fruit (*Citrus japonica* Thunb.), 96% ethanol, n-hexane, ethyl acetate and Butanol. Materials for the phytochemical test are chloroform, chloroform-ammonia, norit, anhydrous acetic acid, concentrated sulfuric acid, Mayer's reagent, iron (III) chloride reagent, magnesium powder, and hydrochloric acid. Materials for activity testing are generic atorvastatin 10 mg (PT. Pratapa Nirmala), standard feed, quail egg yolk, aquadest, NaCMC, ether, multi sera, multi calibrator, aqua pro injection, and triglyceride reagents.

Test Animals:

This study used 25 male white rats (Rattus norvegicus) aged 2-3 months with a body weight of 150-250 grams. This research has conducted ethical clearence in the Ethical Review Board for Medicine and Health Research, Faculty Medicine, University of Riau.

Research Procedure:

Sampling:

The kasturi citrus fruit were obtained from Suka Raya Village, Pancur Batu District, Deli Serdang City, North Sumatra Province. The identification of musk orange plants was carried out in the botanical laboratory of the Biology Department, Faculty of Mathematics and Natural Sciences (FMIPA), Riau University, Pekanbaru.

Preparation of the Ethyl Acetate Fraction and Butanol Fraction of kasturi citrus peel :

The thick ethanol extract of the skin of the citrus fruit was added with aquadest in a ratio of 1: 1 and homogenized, then fractionated using a separating funnel. Fractionation was carried out on three solvents based on different

polarity levels. First it was fractionated with a non-polar3hexane solvent then shaken and left to form two layers consisting of the n-hexane fraction and the water fraction. Fractionation was carried out repeatedly until the extract was completely fractionated. The resulting n-hexane fraction was taken and concentrated by rotary evaporator until the viscous fraction of n-hexane is obtained.The water fraction is then fractionated with a semi-polar ethyl acetate solvent, then shake it and leave it to form two layers consisting of ethyl acetate fraction and water fraction. The results of the ethyl acetate fraction were taken and concentrated using a rotary evaporator to obtain a viscous fraction of ethyl acetate.The water fraction is then fractionated with a polar butanol solvent, then shake it and leave it to form two layers consisting of the butanol fraction and the water fraction. The results of the butanol fraction were taken and concentrated using a rotary evaporator so that the viscous butanol fraction was obtained and after that we did extract and fraction phytochemical screening

High Fat Feed Manufacturing and Induction :

Triglyceride induction in mice using high-fat feed, namely quail egg yolk as much as 10 ml / kgBW [12]. Quail egg yolk was chosen because it has a high fat content compared to other egg yolks, namely 2,139.17 mg / 100gram [13]. High-fat feed is made by separating egg yolks from the white and then condensing them to mice. Induction was carried out orally as much as 10 ml / kgBW which was given once a day for 28 days in all groups of tested animals except for the normal group.

Provision of test preparations :

The test preparation is made by weighing NaCMC and then sprinkling it over hot water in a mortar. Water is used as much as 20 times the weight of NaCMC, then left for about 15 minutes until NaCMC expands, then crushed. After that, the ethyl acetate fraction was added gradually into the mortar while grinding it homogeneously and filling it with distilled water until the limit mark.

For comparison, atorvastatin is made by weighing NaCMC and then sprinkling it over hot water in a mortar. Water is used as much as 20 times the weight of NaCMC, then left for about 15 minutes until NaCMC expands, then crushed. After that, atorvastatin is added gradually into the mortar until it is ground homogeneously and is filled with distilled water until the limit mark.

The test preparation was given orally with a volume of 1% of the body weight of the rats after all groups of experimental animals were induced high-fat feed for 14 days. After that, the treatment was given according to the division of each group for 14 days starting on the 15th day to the 28th day but the high-fat feed was continued until the 28th day. This treatment was carried out after all groups of experimental animals were induced by quail eggs. The rats were given butanol fraction and ethyl acetate fraction of kasturi citrus fruit peel according to the test animal group once a day for 14 days, namely the 15th day to the 28th day.

Blood Sampling and Serum Preparation :

Before taking blood on mice, the mice were anesthetized using ether to relieve pain. Next, blood is drawn using a microhematocrit pipette by rotating the microhematocrit pipette in the orbital vein in the eye area, then the blood that comes out is put in a centrifuge tube, then the blood is left to stand for 30 minutes and centrifuged at 3000 rpm for 10 minutes. After being centrifuged, two layers will be formed where the upper layer is the supernatant and the lower layer is the blood component. The supernatant area was taken with a micropipette with a scale according to the desired amount [14]. Blood was drawn 3 times, namely on the 0th, 15th, and 29th day after treatment. Before taking blood, the rats were fasted for 16 hours.

Measurement of Triglyceride Levels :

easurement of serum triglyceride levels in blood samples in this study used the colorimetric enzymatic test method Glycerol-3-Phospate-Oxidase (GPO) with a photometer (Mindray BA-88A). Measurement of triglyceride levels was carried out by pipetting serum using a micropipette of 10 µl and then put into an Eppendorf tube. Next, 1000 µl of triglyceride reagent was added and homogenized and incubated for 5 minutes at 37ºC. The serum and reagent mixture will be absorbed and measured with a Mindray® BA88-A instrument with a wavelength of 510 nm.

Data Analyzed

Data obtained from observations of triglyceride levels were processed using one-way ANOVA statistical analysis and trials with Tukey's Post Hoc test. Data is presented in tabular form.

RESULT AND DISCUSSION

Ethyl Actatate and Butanol Fraction of The Peel of4Kasturi Citrus

The fractionation results of 2.1 Kg of dry simplicia And from 206.18585 g of thick ethanol extract of the peel of the kasturi citrus fruit (Citrus japonica Thunb.) obtained a thick butanol fraction of 39.1805 g with a yield percentage of 19.0050% and the ethyl acetate fraction was 37.2413 grams with a yield of 18.064%.

Phytochemical Screening

The results of phytochemical screening for the ethyl acetate fraction of the peel of the kasturi citrus fruit (*Citrus japonica* Thunb.) Showed the presence of secondary metabolites of the flavonoid, terpenoids and phenolic groups.

Table 1 : Phytochemical Screening of Ethyl Acetate and Butanol Fraction of Kasturi Fruit peels

Secondary Metabolites	Reagent	Result	Information
Alkaloid	Mayer	-	No white mist is formed
Flavonoid	Logam Mg + HCl (p)	+	Formed in orange color
Phenolic	$FeCl_3$	+	Formed dark green-black
Steroid	Liberman Buchard	-	No blue color formed
Terpenoid	Liberman Buchard	+	Formed in red
Saponin	Air	-	No foam is formed

White rat serum triglyceride levels

he results of the mean serum triglyceride levels of male white rats measured on day 0 of 5 groups of tested animals were in the normal group, the negative group, the positive group, the dose of 250mg / kg Butanol fraction and the ethyl acetate fraction, respectively 83.480; 77,490; 78,179; 85,797; and 89,508 mg / dl, the mean serum triglyceride levels of male white rats measured on the 15th day were 83.84; 152,464; 150,119; 162,589; and 166,240 mg / dl and the mean of serum triglyceride levels of male white rats measured on day 29 were 85,985; 188,415; 83,162; 93,346; and 94,753 mg / dl. The results of the average percentage change in triglyceride levels on the 29th day against the 15th day from the normal, positive group, the dose of 250, mg / kgBW butanol fraction and ethyl acetate fraction were respectively -2.658%; 44,627%; 42,778%; 44.456%; 42% and 44,808%. (table 2 and figure 1)

Based on the results the Post Hoc Tukey statistical test, the percentage change in triglyceride levels on the 29th day against the 15th day showed a significant difference ($p < 0.05$) between the 250 mg / kg body weight butanol fraction and ethyl acetate fraction with the normal control group and The negative control group while the positive control group showed no significant difference ($p > 0.05$), which means that the butanol fraction and ethyl acetate fraction at a dose of 250 mg / kgBW had the same effect as the positive control group in reducing triglyceride levels.

Table 2. Tryglicerides level on day 1st, day 15th, day 29th and percentage change on day 29th against day 15th

Test Group	Number of animal	Day of			percentage change in triglyceride levels on the 29th day against the 15th day
		0	15	29	
Normal	1	87,297	87,839	89,432	-2 %
	2	80,511	80,861	82,932	-3 %
	3	94,497	94,975	96,186	-1 %
	4	81,339	81,594	83,538	-2 %
	5	73,756	73,948	77,835	-5 %
	Mean ± SD	**83,48 ± 7,80**	**83,84 ± 7,93**	**85,98 ± 7,02**	**-3% ± 1,51**
Negative	1	88,348	162,997	194,539	-19 %
	2	68,946	145,378	185,044	-27 %
	3	79,300	154,108	189,600	-23 %
	4	80,670	157,708	191,990	-22 %
	5	70,188	142,128	180,902	-27 %
	Mean ± SD	**77,49 ± 8,02**	**152,46 ± 8,63**	**188,41 ± 5,46**	**-24% ± 3,43**
Positive	1	72,163	142,989	80,893	43 %
	2	83,761	150,603	87,361	42 %
	3	75,158	149,679	84,557	44 %
	4	90,547	168,636	91,630	46 %
	5	69,264	183,688	71,367	49 %
	Mean ± SD	**78,17 ± 8,78**	**150,11 ± 11,46**	**83,16 ± 7,67**	**45% ± 2,77**
250 mg/kgBW Butanol Fraction	1	84,398	160,321	93,794	41 %
	2	78,727	147,226	90,834	38 %
	3	83,120	168,636	85,842	49 %
	4	96,337	172,746	99,882	42 %
	5	86,405	164,016	96,377	41 %
	Mean ± SD	**85,79 ± 6,53**	**162,58 ± 9,78**	**93,34 ± 5,35**	**42% ± 4,08**
250 mg/kgBW Etil Asetat Fraction	1	90.451	175.837	93.765	47%
	2	84.621	146.175	94.434	35 %
	3	91.662	170.739	96.696	43%
	4	86.532	166.852	89.432	46%
	5	94.274	171.599	99.436	42%
	Mean ± SD	**89,51 ± 3,9**	**166,24±11,66**	**94,75 ± 3,71**	**43 % ± 4,57**

High-fat feed triggers high levels of triglycerides in the serum. Quail egg yolk contains saturated fatty acids, saturated fatty acids that are consumed from food are forming triglycerides. After the food undergoes absorption in the small intestine mucosa, saturated fatty acids are activated to become acetyl CoA by thiokinase and ATP enzymes. Acetyl CoA undergoes esterification or the addition of glycerol - 3 - phosphate then forms triglycerides[15]. Based on Anwar's research (2008), every 1% of saturated fatty acid intake can increase 2.7 mg / dl of plasma triglyceride levels[16].

Hypetriglycerides occur due to excess levels of triglycerides. Hypertriglycerides are influenced by food consumption factors such as carbohydrates, fats and alcohol. Therefore to lower blood triglyceride levels apart from dietary fats, carbohydrates are also taken into account. In addition, blood triglyceride levels are also influenced by the activity of the Lipoprotein Lipase enzyme (LPL) which functions to hydrolyze triglycerides into fatty acids and glycerol. Low LPL activity will increase blood triglyceride levels [17].

Figure 1. Percentage Chages of Tryglicerides level on day 29th against day 15th

The decrease in triglyceride levels in this study was due to the pharmacological activity contained in the butanol fraction and the ethyl acetate fraction of the skin of the citrus fruit, namely the content of flavonoids that could potentially affect triglyceride levels in serum. Research conducted by Olivera et al, (2007) explains that flavonoid compounds work by suppressing the activity of the lipoprotein lipase enzyme so that it reduces the production of VLDL in the liver and can inhibit fat mobilization so that triglyceride production can decrease[18]. According to research by Elzbieta et al, (2016) flavonoids can increase hydrolysis with the help of the lipoprotein lipase enzyme found in endothelial cells so that fatty acids and glycerol will be formed[19]. When glycerol enters the active tissue it is converted by enzymes intracellularly into glycerol-3-phosphate which is used for glycolysis or the breakdown of glucose to produce energy[1]. according to Ricardo et al, (2001) flavonoid compounds can inhibit lipolysis in adipose tissue so that it can inhibit triacylglycerol (TAG) esterification in the liver and increase the activity of Lipoprotein Lipase (LPL) so that it can reduce triglyceride levels[20]. The increased LPL enzyme activity will cause the triglycerides in the chylomicron to be hydrolyzed into free fatty acids and stored in adipose tissue[3].

Research Hsu and Yen, 2007 shows that flavonoids and phenolic compounds have natural antioxidant effects that can provide inhibition of intracellular triglyceridesn 3T3-L1 adipocytes[21]. The results showed that flavonoids (routine) and phenolic (o-coumaric acid) had the highest inhibition of glycerol-3-phosphate dehydrogenase (GPDH) activity, an enzyme that plays a role in the synthesis of triglycerides in adipocyte cells, while triterpenoids can provide inhibition of pancreatic lipase. which plays a role in digesting triglycerides from food in the intestine. Pancreatic lipase is responsible for the emulsification of lipids prior to intestinal absorption. Inhibition of pancreatic lipase will inhibit fat absorption and reduce triglyceride levels[22]. The results of the study by Warditiani et al. (2015) that giving terpeniod fraction can reduce triglyceride levels of male white rats induced by high-fat feed[23].

CONCLUSION

From the results of the research that has been done, it can be concluded that the administration of butano and ethyl acetate fraction of the peel of the kasturi citrus fruit (Citrus japonica Thunb.) at a dose of 250 mg / kgBW has a significant effect ($p < 0.05$) compared to the negative control group in reducing triglyceride levels. The serum of male white rats (Rattus norvegicus) also showed a decrease in triglyceride levels which was not significantly different ($p > 0.05$) with atorvastatin as an antihyperlipidemic drug.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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