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THE EFFECTIVENESS OF ETHANOL EXTRACT OF JAMBLANG LEAVES (*Syzygium cumini* L.) IN INCREASING HDL LEVELS IN WISTAR RATS MODELS OF METABOLIC SYNDROME

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Abstract

One of the characteristics of metabolic syndrome (MetS) is the low high-density lipoprotein (HDL) levels. Jamblang leaves (*Syzygium cumini* L.) contain various phytochemicals, which have antihyperglycemic, antihyperlipidemic, and antioxidant properties. This study aims to demonstrate the effectiveness of ethanol extract of jamblang leaves in increasing HDL levels in the Wistar rats model of MetS. A pretest-posttest with a control group design was conducted using 30 male Wistar rats, divided into five groups randomly, with six rats for each group. Here, KN means normal control group, K- negative control group, and P1, P2, and P3: treatment groups that were administered the 100 mg/kg/day, 150 mg/kg/day, and 200 mg/kg/day of ethanol extract of jamblang leaves for 28 days, respectively. The rat MetS model was developed by administering the high-fat fructose diet and streptozotocin-nicotinamide. The data were analyzed using paired t-test and one-way ANOVA (α=0.05). This study found that extract administration in P2 and P3 increased HDL levels significantly, but not with the P1 group. However, HDL levels in P1 were significantly higher compared to the K- group. Moreover, increasing the dose was significantly followed by higher HDL levels, although the highest dose did not reach the HDL level as in the KN group.

Keywords: *Jamblang leaves; HDL; Metabolic syndrome*

1. Introduction

Metabolic syndrome (MetS) still becomes a health burden globally. It coexists with urbanization, excessive calorie intake, alongside increased incidence of obesity and a sedentary lifestyle (Suhaema & Masthalina, 2015). This syndrome increases the risk of atherosclerosis, cardiovascular diseases, diabetes mellitus type 2, and stroke (Rochlani, Pothineni, Kovelamudi, & Mehta, 2017; Suhaema & Masthalina, 2015).

The prevalence of MetS is hard to determine due to the different criteria of diagnosis (Suhaema & Masthalina, 2015). One of the most frequent diagnostic tools is the National Cholesterol Educational Program Adult Treatment Program III (NCEP ATP III) criteria, which is diagnosed based on three of five syndromes, including hypertension, hyperglycemia, central obesity, hypertriglyceridemia, and low high-density lipoprotein (HDL) levels (Kaur, 2014; Rochlani et al., 2017).

Low HDL level is associated with the risk of coronary heart disease (CHD). An increase of 1 mg/dL in plasma HDL-cholesterol levels can reduce the risk of CHD by 2% in men and 3% in females. The primary role of HDL is reverse cholesterol transport, in which the excess amount of cholesterol is removed from the peripheral blood and transported back to the liver for excretion (Rampengan, 2015).

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One of the methods to increase the HDL levels in MetS is using natural components derived from plant extracts (Rochlani et al., 2017). The natural plant that has potency in increasing HDL levels in MetS is the jamblang plant (*Syzygium cumini* L.). Jamblang leaves contain flavonoids which have potential as an antioxidant (Ramya, Neethirajan, & Jayakumararaj, 2012). Saponin enhances flavonoid activity (Chhikara et al., 2018). Another antioxidative feature in jamblang leaves is the phenolic acid, which reduces the low-density lipoprotein (LDL) and triglyceride/HDL cholesterol ratio (Sah & Verma, 2011). Furthermore, jamblang leaves have B-sitosterol and anthocyanin, which act as antioxidants (Joshi, Paudel, & Upreti, 2019; Priska, Peni, Carvallo, & Ngapa, 2018). Jamblang leaves were also reported to contain triterpenoid, with its free radical scavenging activity (Ramya et al., 2012) and tannin, an antihyperglycemic agent (Freitas, 2018).

Studies investigating the effect of ethanol extract of jamblang leaves on HDL levels in MetS have been few. Therefore, modeling MetS in Wistar rats and demonstrating the effectiveness of ethanol extract of jamblang leaves in increasing HDL levels is an interesting feat. The MetS model is designed by inducing the rat with a high-fat fructose diet (HFFD), alongside injecting streptozotocin (STZ) and nicotinamide (NA).

2. Method

This study was an experimental laboratory using pretest-posttest with a control group design. The study was conducted from July to September 2022 at Pusat Studi Pangan dan Gizi (PSPG) of Universitas Gadjah Mada in Yogyakarta. The samples were Wistar strain of white rats (*Rattus novergicus*), aged eight weeks, and weighed 150 -200 grams. Purposive sampling was used in this study. The sample size was calculated using the Federer formula, in which five groups needed five rats for each. However, to anticipate exclusion during the study, each group added with one extra rat, resulting in 6 rats. Thus, the total sample was 30 rats. The group of this study consisted of the normal control group (KN), negative control group (K-), and treatment groups (P1, P2, and P3).

The KN group was defined as normal rats which did not receive any treatment. In comparison, the K- group was of MetS model rats without any treatment. Finally, the treatment groups: P1, P2, and P3, were MetS model rats that received ethanol extract of jamblang leaves with the dose of 100 mg/kg/day, 150 mg/kg/day, and 200 mg/kg/day, respectively, for a consecutive 28-day period.

Before developing the MetS model rats (inducing HFFD and STZ-NA), seven-day adaptations were involved. On day 8 post-adaptation, the rats were randomly divided into five groups and weighed. The initial body weight (BW) was recorded to calculate the percentage of increase in body weight after the inductions of HFFD and STZ-NA. These inductions were expected to increase body weight and induce dyslipidemia and hyperglycemia. The HFFD induction was done for a consecutive 24-day period (from day 8 until day 32), while the STZ-NA induction was on day 29. The HFFD was composed of 2 ml coconut oil, 0.2 g/kg colic acid, 4 g/kg cholesterol, and 0.36 g/200 g fructose. The HFFD was fed by oral gavage with the composition of 1% of the rat's BW for each MetS model group (K-, P1, P2, and P3 group). Meanwhile, STZ (diluted with buffer citrate 0.1 M, pH 4.5) was administered by intraperitoneal injection with a single dose of 45 mg/kg. Fifteen minutes before STZ administration, NA (diluted with normal saline) was injected intraperitoneally with a single dose of 110 mg/kg.

The night before the 33rd day, the rats fasted overnight for 8 hours. On day 33 (induction with HFFD for 24 days and three days post-STZ-NA injection), rats were weighed, and their blood was collected from retro-orbital venous to measure fasting blood glucose (FBG), total cholesterol, triglyceride (TG), and HDL. This method was used to determine the success of developing the MetS model before treatment. The body weighing was done on day 33 to calculate the differences in the rats' BWs between day 8 (before inducing with HFFD) and day 33 (after inducing with HFFD for 24 days and STZ-NA on day 29). MetS diagnoses were confirmed in the models if the level of FBG > 100 mg/dL, total cholesterol > 110 mg/dL, TG > 150 mg/dL, HDL < 35 mg/dL, and body weights increase by a minimum of 8% of the initial weight (Suman, Ray Mohanty, Borde, Maheshwari, & Deshmukh, 2016).

In this study, ethanol extract of jamblang leaves was produced using the maceration method with ethanol solvent 96%. The dried jamblang leaves were obtained from Wonopolo

Village, Gulurejo Sub District, Kulonprogo Regency, Yogyakarta Province. The extract was manufactured at Laboratorium Penelitian dan Pengujian Terpadu (LPPT) unit 1 Universitas Gadjah Mada, Yogyakarta. The extract was divided into three doses: 100 mg/kg/day (for the P1 group), 150 mg/kg/day (for the P2 group), and 200 mg/kg/day (for the P3 group). It was given for 28 days concurrently, starting after the induction of HFFD and STZ-NA. The extract was given orally in suspension solution form using a mixture of 0.5% CMC-Na by oral gavage. The dose of jamblang leaves extract was based on a previous study by (Ningrum, Salim, & Balqis, 2017), which observed the effect of these extracts on the histopathology of the liver of rats in the diabetes mellitus models.

In our study, the blood HDL levels were measured twice, before and after the 28-day treatment with jamblang leaves ethanol extract. The blood was collected from retro-orbital venous tissues in the rats' eyes. Blood serum HDL levels were measured using colorimetric enzyme assay and perspiration and stated in the unit of mg/dL.

Data were analyzed with the paired t-test to measure the HDL levels difference between the pretest and posttest for each group. Moreover, one-way ANOVA was performed to analyze the differences in HDL levels among all groups during the pretest and posttest. Should any significant difference be found in one-way ANOVA, the post hoc test (Tukey HSD test) will be performed. The significance level of this study was $p<0.05$

3. Results and Discussion

The administration of HFFD and STZ-NA inducted MetS into the white rat

Table 1. The mean concentration of FBG, Total Cholesterol, TG, and HDL after induction of HFFD and STZ-NA

Group	FBG (mg/dL)	Total Cholesterol (mg/dL)	TG (mg/dL)	HDL (mg/dL)
KN	67.9±1.70	91.1±2.64	74.12±1.76	83.09±1.43
K-	275.52±4.92	185.16±6.49	129.67±6.42	24.88±1.83
P1	271.22±4.98	180.68±4.97	126.52±3.52	24.80±1.91
P2	273.89±3.89	179.62±5.68	127.02±2.94	25.04±1.60
P3	268.95±5.41	183.98±6.14	127.90±5.43	25.37±2.05

Based on Table 1, the K-, P1, P2, and P3 groups had FBG > 100 mg/dL, total cholesterol > 110 mg/dL, TG < 150 mg/dL, and HDL < 35 mg/dL, respectively. In addition, table 2 showed that the weight gain of rats in the K-, P1, P2, and P3 groups was more than 8% after the induction of HFFD and STZ-NA.

Table 2. The mean of body weight before and after induction of HFFD and STZ-NA

Group	BW (g) Before induction	BW (g) After induction	The addition of BW(%)
KN	168.67±2.80	197.67±2.16	17%
K-	170.83±4.96	210.17±5.53	23%
P1	172.5±4.51	211.33±4.63	22%
P2	167.17±3.49	206.50±2.74	24%
P3	171.33±3.98	210.67±4.13	23%

Hence, the administrations of HFFD and STZ-NA on the K-, P1, P2, and P3 groups successfully induced MetS in the rats. According to (Suman et al., 2016), rrats experience MetS if they have a minimum of 4 out of 5 criteria: the levels of FBG > 100 mg/dL, total cholesterol > 110 mg/dL, TG > 150 mg/dL, HDL < 35 mg/dL, and a minimum of 8% of weight gains compared to initial body weights. Hence, although the TG was below 150 mg/dL, the study fulfilled the four criteria: FBG > 100 mg/dL, total cholesterol > 110 mg/dL, HDL < 35 mg/dL, and rats' weight gains of more than 8% of the initial body weights (as stated in table 1 and table 2).

The HDL levels before and after the administration of jamblang leaves

Table 3. The mean HDL Levels in Rats before and after extract of jamblang leaves

Group	HDL (mg/dL)		Difference of HDL Pre-Post Test (mg/dL)
	Pretest	Posttest	
KN	83.09 ± 1.43	81.70 ± 1.27	-1.40 ± 0.60
K-	24.88 ± 1.83	24.07 ± 2.22	-0.81 ± 0.67
P1	24.80 ± 1.91	54.24 ± 1.77	29.44 ± 2.70
P2	25.04 ± 1.60	68.14 ± 1.27	43.10 ± 1.68
P3	25.37 ± 2.05	76.50 ± 1.57	51.13 ± 2.82

Table 3 and Figure 1 displayed the changes in HDL pretest and posttest levels with ethanol extract of jamblang leaves, respectively, for each group. In the KN group, the HDL levels were within the normal range, although the levels

slightly decreased in the posttest. Meanwhile, the K- group had HDL levels below normal, which also slightly decreased in the posttest. Finally, the treatment groups (P1, P2, P3) showed increased HDL levels in the post-tests. The most significant increase was in the P3 group, which was administered with the highest ethanol extract of jamblang leaves (200 mg/kg/day).

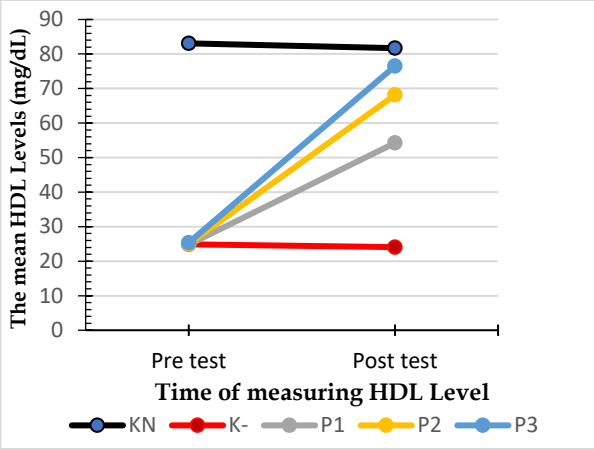

Figure 1. *The changes in rat HDL levels from pretest and posttest*

In the beginning, the HFFD induction succeeded in establishing the MetS model in rats, which was confirmed by a reduction in HDL levels. Before the administration of jamblang leaves ethanol extracts, low HDL levels (< 35 mg/dL) were seen in the MetS model groups (K-, P1, P2, P3) (table 3). However, after the extract treatment for 28 days consecutively with the dose of 100 mg/kg/day (for the P1 group), 150 mg/kg/day (for the P2 group), and 200 mg/kg/day (for the P3 group), increases in HDL levels could be seen (figure 1).

Table 4. Paired-t Test of HDL Levels

Group	P-value
KN	0.002*
K-	0.031*
P1	0.000*
P2	0.000*
P3	0.000*

** Significantly different*

Table 4 showed the MetS model groups obtaining 100 mg/kg/day (P1), 150 mg/kg/day (P2), and 200 mg/kg/day (P3) had significantly higher HDL levels in the posttest than in the pretest. It is concluded that the P1, P2, and P3 groups had significant increases in HDL levels after the extract administrations. In addition, the P3 group received the highest increase in HDL level post-test (table 3).

According to Table 4, HDL levels in the posttest were significantly lower in the KN and K- groups. Although both groups had decreased HDL levels, in the posttests they were still within the normal range in the KN Group, while stayed lower in K- Group.

Table 5. One Way ANOVA test of Pretest and Posttest

Time of HDL Levels Measurement	P-value
Pretest	0.000*
Posttest	0.000*

**Significantly difference*

Table 6 showed that HDL levels were significantly lower in the MetS model groups (K-, P1, P2, P3) compared to the normal control group (KN) on the pretests before the extract treatment. However, no significant difference was evident among the MetS model groups. Hence, the K-, P1, P2, and P3 groups had similar HDL levels before receiving jamblang leaves ethanol extract.

Table 6. Tukey HSD Test of Pretest and Posttest

Comparison between groups	P-value of pretest	P-value of posttest
KN - K-	0.000*	0.000*
KN - P1	0.000*	0.000*
KN - P2	0.000*	0.000*
KN - P3	0.000*	0.000*
K- - P1	1.000	0.000*
K- - P2	1.000	0.000*
K- - P3	0.989	0.000*
P1 – P2	0.999	0.000*
P1 – P3	0.980	0.000*
P2 – P3	0.998	0.000*

**Significantly difference*

Moreover, table 6 displayed significant differences in HDL levels among all of the groups after the extract treatment (posttest). The MetS groups who received extract treatment (P1, P2, P3) had significantly higher HDL levels than the negative control group (K-). However, the concentrations of HDL were still significantly lower compared to the normal control group (KN).

The administration of ethanol extract of jamblang leaves induced HDL levels in white rats of the MetS model

The most important finding was the significant increases in HDL levels among the P groups (P1, 2, and 3) after 28-day administrations of jamblang leaves ethanol extract with the dose of 100 mg/kg/day (in P1), 150 mg/kg/day (in P2), and 200 mg/kg/day (in P3). This result was shown in the paired t-test, which displayed a significant difference in HDL levels before and after the administration of the extract, with a p-value= 0.000 (table 4). Moreover, the HDL post-test levels in P1, P2, and P3 groups were significantly higher compared to the MetS model without treatment (K-). This can be seen from the post hoc Tukey HSD test, which analyzed the difference of the P1 and K-, P2 and K-, alongside P3 and K- during the posttest (p-value= 0.000). Although HDL levels were increased post treatment with the doses, any of the increases were still unable to reach that of the normal control state. This result can be seen from the post hoc Tukey HSD test, which compared the P1 with KN, the P2 with KN, and the P3 with KN during the post-test (p-value= 0.000).

Also, the incremental dose of jamblang leaves extracts, namely 100 mg/kg/day, 150 mg/kg/day, and 200 mg/kg/day in this study, showed a significant effect in increasing HDL levels in the model MetS rats. This can be seen from the Tukey HSD post hoc test results, which compared groups P1 and P2, P1 and P3, and P2 and P3 at the posttest (p-value= 0.000). It can be suggested that the higher the dose given, the higher the increase in HDL levels. As mentioned previously, the HDL levels of these three groups cannot reached the HDL level in KN group. This might also suggest that the dose given, even the 200 mg/kg/day, was not optimum enough to reach the therapeutic effect in increasing HDL. Hence, increasing the dose might be an option in the further studies. Previous studies found no sign of acute or chronic toxicity or behavioural changes in rats or mice that had been administered orally with *Syzygium cumini* L. (Qamar et al., 2022; Silva et al., 2012). Based on Silva et al. (2012), no sign of acute toxicity or death was reported when the rats and mice were administered orally with the hydroalcoholic extract of *Syzygium cumini* L. with a dose of 2 and 6 g/kg, respectively. Previous study, also, found that a dose of 0.05 g/kg, 0.1 g/kg, and 0.25 g/kg did not show any behavioural changes, body weight changes, and mortality when administered per oral chronically in rats (Silva et al., 2012).

Similarly, another study displayed no acute toxicity was found during the administration of 2000 mg/kg and 3000 mg/kg in rats for 14 days, and no sub-acute toxicity was reported during the administration of *Syzygium cumini* L. with doses up to 750 mg/kg and 1500 mg/kg in rats for 28 days (Qamar et al., 2022). Hence, increasing the dose higher was still considered safe.

The ethanol extract of jamblang leaves, nevertheless, increased HDL levels in the MetS model of rats. This owes to the various phytochemicals with their antioxidant properties. These phytochemicals include flavonoids (Ramya et al., 2012). Flavonoids act as antioxidants by becoming H+ ion donors (chelating agents) that bind to free radicals, suppressing the activity of xanthine oxidase, protein kinase, cyclooxygenase, and NADPH oxidase (Banjarnahor & Artanti, 2015). B-glycoside, the main constituent of flavonoids, prevents insulin resistance (increases insulin sensitivity) and reduces free radical activity (ROS) (Janabi et al., 2020).

Besides flavonoids, jamblang leaves contain quercetin, a flavonoid derivative compound. Quercetin is a potent scavenger to suppress ROS and acts as an anti-inflammatory agent by inhibiting the activity of TNF-α, IL-1B, and IL-6 (acute inflammatory cytokines and atherogenic signalling carriers) (Štochmaľová, Sirotkin, Kádasi, & Alexa, 2021). Another flavonoid-derived compound is the flavone tricetin, which can inhibit the release of IL-1B (a cytokine that triggers vascular inflammation) and suppress the production of ROS in the vascular endothelium (Cai, Zhang, Hou, & Gao, 2020).

In addition to flavonoids and their derivatives, jamblang leaves contain phenolic

acid. This component can improve the profile of glucose, total cholesterol, and Free Fatty Acid (FFA) by increasing insulin sensitivity (França et al., 2019). Gallic acid and ellagic acid, the main phenolic acid compounds in jamblang leaves, have been documented as antioxidants that can reduce the ratio of TG to HDL and reduce LDL levels (Sah & Verma, 2011).

Various phytochemicals such as triterpenoid, saponin, tannin, steroid, and anthocyanin are also found in jamblang leaves. Triterpenoid act as anti-inflammatory agents by increasing the activity of free radical scavengers (Ramya et al., 2012). Saponin can inhibit glucagon activity, which strengthens the activity of flavonoids to stimulate insulin sensitivity (Chhikara et al., 2018). Tannin has antihyperglycemic properties by stimulating glycogenesis (Freitas, 2018). B-sitosterol, the main compound of steroid in jamblang leaves, plays a role as an antioxidant (Joshi et al., 2019). The anthocyanin compounds also support the antioxidant function of jamblang leaves (Priska et al., 2018).

In summary, it can be concluded that phytochemicals in the ethanol extract of jamblang leaves can function as an antioxidant, anti-inflammatory, and agents that increase insulin sensitivity (reducing insulin resistance). These three functions can increase HDL levels in the model of MetS in white rats. The antioxidant properties will capture free radicals (e.g., ROS), so it can lower the level of oxidative stress (Janabi et al., 2020). In turn, the decreased oxidative stress levels will reduce insulin resistance (Besse-Patin & Estall, 2014). Likewise, the anti-inflammatory effect will lower insulin resistance (Cai et al., 2020). The lessening of insulin resistance will decrease the activity of hormone-sensitive lipase (HSL) in fat cells; thus, the lipolysis of triglycerides in fat tissue declines. The decrease of lipolysis will suppress the excessive formation of free fatty acids (FFA) in blood circulation. In the absence of excessive FFA, the uptake of FFA by the liver as material for TG formation will be reduced. In that case, the availability of TG as a component of the Very Low-Density Lipoprotein (VLDL) lipoprotein molecule is also declined, so that the formation of triglyceride rich VLDL (large VLDL) will also decrease. As the large VLDL is lessened, there will be a reduced of exchange between TG in large VLDL with cholesterol ester contained in HDL lipoproteins. This small exchange process will suppress the formation of HDL lipoproteins rich in TG and low in cholesterol ester. It has been known that HDL lipoproteins that are rich in TG and poor in cholesterol ester are easily catabolized by the kidneys, causing a drop in HDL levels in the blood. Thus, reducing this HDL formulation will lessen the HDL catabolism by the kidney, and prevent a low HDL level (Jim, 2013; Rampengan, 2015).

A previous study was carried out on jamblang plants to reduce the LDL levels in the blood (Ferry SP, Manurung, & Puspawati, 2015). This study proved a significant effect of anthocyanin on the skin of jamblang fruit (*Syzygium cumini)* in reducing LDL levels and increasing HDL levels of the hypercholesterolemic Wistar rats.

Furthermore, another former study investigated the effect of ethanol extract from jamblang plant pulp on the lipid profile of hyperlipidemic Wistar rats induced with triton x-100 (Singh, Singh, Sagar, & Das, 2018). This study showed a significant effect of the extract in improving the lipid profile of hyperlipidemic rats, including a significant increase in HDL levels.

Nevertheless, there are limitations to this study. First, this study did not conduct phytochemical tests on the extracts. Hence, it cannot distinguish the active substances involved. In addition, the variation in the dose of the extract used was limited to three levels, where the highest dose had not been able to give the same results of HDL levels as the normal control group. Finally, the MetS parameters studied in this study were limited to blood HDL levels.

4. Conclusion and Suggestion

In conclusion, our findings confirm the administration of jamblang leaves ethanol extract (*Syzygium cumini L.*) significantly increased HDL

levels in the MetS model Wistar rats. Further studies are encouraged to run phytochemical tests on the extracts to identify more active components affecting the results. It is also necessary to conduct research with more varied levels of extract dose to see which dose is capable of reaching the same levels as those in the normal control group. Lastly, further research on the effect of jamblang leaves extract needs to include the other parameters in MetS to develop an extract that can actually be used for MetS therapy in humans.

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