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The Effect of Ethanol Extract of *Carica papaya* Seed towards Lipid Profile on Rats Induced Rifampicin and Isoniazid

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Rifampicin one of the most commonly used front-line drugs in antituberculosis therapy, has been known to be hepatotoxic. The oxidative stress that is formed in the mitochondria due to rifampicin and isoniazid causes an imbalance in lipid metabolism. This study aims to determine the effect of lowering total cholesterol, triglyceride, and LDL levels and increasing HDL levels of papaya seed ethanol extract in rats induced by rifampin and isoniazid.
Study design: This study is experimental study.
Methodology: This study was divided into 9 groups including normal group, negative group 1, 2, 3, positive 1, 2, treatment group I (EECP 100 mg/kgbw), treatment group II (EECP 300 mg/kgbw), and treatment group III (EECP 500 mg/kgbw). Rifampicin (50 mg/kgbw), isoniazid (50 mg/kgbw), and EECP were given 28 days, on day 29 rats were dissected and blood was taken and the total cholesterol, triglyceride, LDL and HDL levels were measured.
Results: The results showed that the ethanol extract of papaya seeds at a dose of 100 mg / kgbb, 300 mg / kgbb, and 500 mg / kgbw could reduce levels of total cholesterol, triglycerides, LDL and increase HDL levels. The dose of 500 mg / kgbw was not statistically significant (P> 0.05) with the normal group.

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Conclusion: Ethanol extract of *Carica papaya* has a potential effect of preventing the destruction of lipid metabolism effect by reducing the LDL, Trygliseride, Cholesterol Total, and increasing the level of HDL.

Keywords: Rifampicin; isoniazid; Carica papaya seed; lipid profile.

1. INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease and is still one of the most serious problems for humans worldwide, which is caused by the bacteria known as *Mycobacterium tuberculosis* and is characterized by fever and cough [1]. TB disease is a global problem, and still the main infectious disease in Indonesia [2]. Indonesia, with a large population, also has a large number of people with tuberculosis, including the top five in the world. Every year around 850 thousand people with tuberculosis in Indonesia, and 13 people die from tuberculosis every hour [3]. In 2016, Indonesia was ranked second in the world with the most TB sufferers [4] (Ministry of Health, 2017). Report to the World Health Organization (WHO) in 2014, the incidence of pulmonary tuberculosis in 2013 was estimated at 450,000 people, 170,000 of whom died [5,6].

In the treatment of TB, the first-line therapy is Rifampin, in combination with Isoniazid (INH), Ethambutol (ETB), and Pyrazinamide (PZA). The most common side effects of Rifampicin are hepatotoxicity [7], disseminated intravascular coagulation (DIC) [8], nephrotoxicities such as acute tubular necrosis and interstitial nephritis (IN) have also been reported7. combination TB drugs can increase the risk of hepatocellular carcinoma in patients with cirrhosis of the liver [9].

The liver has an essential role in the metabolic process of sugar, protein, and free fatty acids (FFA). LDL-cholesterol which is harmfull and unhealthy cholesterol can accumulate in the arteries and form fat and fat deposits which will form plaque which eventually causes blockage in the blood vessels in the heart and brain organs, HDL which is a type of good healthy cholesterol will transport excess cholesterol out of the artery to the liver for the process of removing it from the body [10]. The liver is known to be involved in the synthesis of triglycerides and cholesterol which are synthesized from acetyl CoA substrates which are produced through fatty acid oxidation, therefore it is necessary to check blood cholesterol levels [11].

Papaya seeds are rich in polyphenols, flavonoids, triterpenoids, tannins, saponins, alkaloids [12], anthraquinones [13]. The ethyl acetate fraction from papaya seed extract had the strongest antioxidant activity, and the n-butanol fraction had the second strongest antioxidant activity. DPPH activity and hydroxyl free radical activity of ethyl acetate fraction was stronger than ascorbic acid [14].

Based on the description above, rifampicin and isoniazid can caused hepatotoxicity leading to distraction of lipid metabolism. *Carica papaya* seed may prevent the distruction of lipid metabolism.

2. MATERIALS AND METHODS

2.1 Materials

Rifampicin (pharmaceutical chemistry), INH (pharmaceutical chemistry), Curcuma FCT (pharmaceutical chemistry), Na CMC 0.5%, Dialab® ALT reagent kit, Dialab® AST reagent kit, rutin (Sigma Aldrich), alkaliphosphatase kit, gamma gtkit , and kits of bilirubin, zinc powder, toluene, dyestuffs (hematoxylin and eosin). Microplate Reader, pH meter (OHAUS Starter300 Portable) Beaker glass (IWAKI CTE33), Multiskan Go Reader (Thermo Fisher Scientific 1510), analytical measure, Eppendorf tube, 1 ml vial, Spatula, Micropipette (1-10 L, 50-200 L , 100-1000 L) (Eppendorf), Thermometer, automated plate washer, Tumeric, Vitamin E, Ketamine (Sigma P-4417).The animalsused in this study were male rats 150-200 g. Before this study began, the test animals were acclimatized for one week under room temperature conditions (22-25°C), under a 12 hour light / dark cycle, given pellets and drinking water add libitum.

2.2 Extraction of *Carica papaya*

500 g of papaya seed powder was put into a reagent bottle and macerated using 96% ethanol solvent with a volume ratio between powder and solvent that is 1: 3 w/v. This mixture is shaken using a shaker for ± 48 hours at a speed of ± 200-250 rpm. Furthermore, the papaya seed

ethanol extract solution is evaporated using a rotary evaporator at temperatures ranging from 45-50°C, after the rotary evaporator the solution is placed in a water bath to evaporate the remaining solvent that is still in the extract.

2.3 Evaluation of Lipid Profile Induced Rifampicin and Isoniazid

Rats Wistar as subjects, with a length of study for 28 days15. The in vivo test in the experiment used 27 healthy rats weighing about 200 g ± 10%, divided into 9 groups and each group consisting of 3 rats, namely: information: EECP (Ethanol extract of *carica papaya* seed), Rif (Rifampicin), INH (Isoniazid).

Induction of liver damage using the maximum dose of Rifampin + INH dose 50 mg/kg/oral/day respectively [15,16]. EECP in experimental rats, group 1 was 100 mg/kg, group 2 was given 300 mg/kg, and Group 3 was given 500 mg/kg body weight every day for 28 days. On the 29th day, the rats were operated on, and blood was taken from the heart and then measured the levels of LDL, HDL, Cholesterol Total, and Triglycerides.

3. RESULTS AND DISCUSSION

Phytochemical screening of ethanol extract of *carica papaya* of showed the positive result of flavonoids, tannins, saponins, glycosides, alkaloid, and steroids.

In this research, conducted an examination of total cholesterol from the blood of rats. Results of total cholesterol and triglycerides level are obtained can be seen in Table 2.

Based on Table 2, it shows that the negative control group-3 with total cholesterol of 326.33 ± 17.82 mg/dl was significantly different ($p < 0.05$) from the normal group with total cholesterol of 67 ± 1.632 mg/dl. The positive control group-2 with total cholesterol of 69.66 ± 41.109 mg/dl was not significantly different ($p > 0.05$) with the normal group. Treatment group I with a total cholesterol value of 274 ± 12.56 mg/dl was significantly different ($p < 0.05$) from the normal group. Treatment group II with total cholesterol 157.33 ± 8.49 mg/dl was significantly different ($p < 0.05$) from the normal group. Treatment group III with a total cholesterol value of 74.33 ± 3.85 mg/dl was not significantly different ($p > 0.05$) with the

Table 1. Experimental design

Group	Inducer	Treatment
Normal	(-)	Na-CMC 0,5%/oral
Negative-1	Rif 50 mg/kgBW/oral	Na-CMC 0,5%/oral
Negative-2	INH 50 mg/kgBW/oral	Na-CMC 0,5%/oral
Negative-3	Rif +INH @50mg/kgBW/oral	Na-CMC 0,5%/oral
Positive-1	Rif +INH @50mg/kgBW/oral	Curcumin FCT mg 4,32 mg/oral
Positive-2	Rif +INH @50mg/kgBW/oral	Simvastatin 0,18 mg/oral
Group-1	Rif +INH @50mg/kgBW/oral	EECP 100 mg/kgBW/oral
Group-2	Rif +INH @50mg/kgBW/oral	EECP 300 mg/kgBW/oral
Group-3	Rif +INH @50mg/kgBW/oral	EECP 500 mg/kgBW/oral

Table 2. Total cholesterol and triglycerides level

Group	Mean Total Cholesterol ± standard deviation (mg/dL)	Triglycerides ± standard deviation (mg/dL)
Normal	67 ± 1,632#	71,33 ± 2,62
Negative-1	273,33 ± 23,098	190,33 ± 32,67
Negative-2	293 ± 10,801	195,33 ± 32,60
Negative-3	326,33 ± 17,82	213,33 ± 14,079
Positive-1	70,66 ± 4,02#*	73,66 ± 4,78
Positive-2	69,66 ± 41,109#*	66,33 ± 9,03
Group-1	274 ± 12,56	186,33 ± 9,03
Group-2	157,33 ± 8,49#	133 ± 9,09
Group-3	74,33 ± 3,85#*	61,33 ± 12,22

Post tukey test p<0,05 #: has a significant different with negative 1, 2, 3 group
*P,0,05 *: No significant different with normal*

Table 3. HDL and LDL level

Group	Mean Low density lipoprotein ± standard deviation (mg/dL)	High density lipoprotein ± standard deviation (mg/dL)
Normal	20,33 ± 1,24	51,66 ± 2,04
Negative-1	107,67 ± 9,97	32 ± 2,94
Negative-2	111,67 ± 14,65	30 ± 3,59
Negative-3	114,33 ± 18,57	23 ± 2,94
Positive-1	22,33 ± 3,29	57,33 ± 5,43
Positive-2	23,33 ± 3,29	53,66 ± 4,02
Group-1	89,66 ± 4,10	29,66 ± 6,59
Group-2	56,67 ± 7,58	34,66 ± 4,92
Group-3	27 ± 2,94	57,66 ± 1,69

Post tukey test p<0,05 #: has a significant different with negative 1, 2, 3 group
*P,0,05 *: No significant different with normal*

normal group. Based on Table 3, it shows that the negative control group-3 with triglycerides 213.33 ± 14.079 mg/dl was significantly different (p <0.05) from the normal group with triglycerides 71.33 ± 2.62 mg/dl. The positive control group-2 with triglycerides 66.33 ± 9.03 mg/dl was not significantly different (p> 0.05) from the normal group. Treatment group I with triglyceride value 186.33 ± 9.03 mg/dl was significantly different (p <0.05) from the normal group. Treatment group II with triglyceride levels of 133 ± 9.09 mg/dl was significantly different (p <0.05) from the normal group. Treatment group III with a triglyceride value of 61.33 ± 12.22 mg/dl was not significantly different (p> 0.05) with the normal group. LDL and HDL level can be seen in Table 3.

Based on Table 3, it shows that the negative control group-3 with HDL 23 ± 2.94 mg/dl was significantly different (p <0.05) from the normal group with HDL 20.33 ± 1.24 mg/dl. Positive control group-2 with HDL 53.66 ± 4.02mg / dl was not significantly different (p> 0.05) with the normal group. Treatment group I with HDL value of 29.66 ± 6.59 mg/dl was significantly different (p <0.05) from the normal group. Treatment group II with HDL levels 34.66 ± 4.92 mg/dl was significantly different (p <0.05) from the normal group. Treatment group III with HDL value of 57.66 ± 1.69 mg/dl was not significantly different (p> 0.05) with the normal group. Based on Table 3, it shows that the negative control group-3 with LDL 114.33 ± 18.57 mg/dl was significantly different (p <0.05) from the normal group with LDL 20.33 ± 1.24 mg/dl. Positive control group-1 with LDL 22.33 ± 3.29 mg / dl was not significantly different (p> 0.05) from the normal group. Treatment group I with an LDL value of 89.66 ± 4.10 mg/dl was significantly different (p <0.05) from the normal group. Treatment group II with LDL levels of 56.67 ± 7.58 mg/dl was significantly different (p <0.05) from the normal group. Treatment group III with an LDL value of 27 ± 2.94 mg/dl was not significantly different (p> 0.05) with the normal group.

Papaya seeds contain lots of flavonoids. Flavonoids themselves are compounds that act as antioxidants. The antioxidant mechanism of flavonoids is to capture ROS directly, prevent ROS regeneration, and indirectly increase the antioxidant activity of cellular antioxidant enzymes [17]. Flavonoids are the most effective compounds as a scavenger of reactive species, for example, super dioxide, peroxyl radicals, and peroxynitrite by transferring H + atoms. Prevention of the formation of ROS by flavonoids is carried out in several ways, namely inhibiting the action of the enzymes xanthine oxidase and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, as well as chelating metals (Fe2+ and Cu2+) to prevent redox reactions that can produce free radicals, stating that flavonoids are antioxidants plays a role in protecting lipophilic antioxidants so that they can strengthen cellular antioxidants [18]. Several studies have also shown that the antioxidant activity of flavonoids is closely related to the prevention of several diseases, such as cardiovascular disease, cancer or tumours and liver disease [19]. Another function of flavonoids is to reduce blood cholesterol levels because flavonoids work to increase HDL cholesterol by increasing the production of apo A [20].

Papaya (*Carica papaya* L.) contains primary metabolite compounds and secondary metabolite compounds. Primary metabolite compounds in papaya leaves are vitamins C and E. Research conducted by Nuehaeni found that papaya leaves contain secondary metabolite compounds, namely flavonoids, saponins,

polyphenols and alkaloids [21]. Research conducted by Sudarwati found that papaya leaves taken from KarangPandan Village, Karanganyar Regency, Central Java contain secondary metabolites of alkaloids, saponins, and flavonoids [22]. The seed content in papaya fruit is approximately 14, 3% of the whole papaya fruit. It contains high levels of unsaturated fatty acids, namely oleic and palmitic acids. Apart from containing fatty acids, papaya seeds are known to contain other chemical compounds such as phenols, alkaloids, terpenoids, and saponins.

Rifampicin, one of the most commonly used front-line drugs in antituberculosis therapy, has been known as hepatotoxic [23]. Two in vitro studies showed that rifampin caused direct toxic injury to mouse hepatocytes. Several *in vivo* studies have found that rifampin plus isoniazid induces apoptosis of hepatocytes in rodents [24]. The mechanism by which rifampin induces liver damage is not clear. A previous study showed that oxidative stress in mitochondria is involved in the pathogenesis of rifampin plus isoniazid-induced apoptotic liver cell injury in mice [25]. According to a report from our laboratory, rifampin causes intrahepatic cholestasis through changes in the integrity of the ZO-1 hepatocytes and occlusion. In this study, the administration of rifampicin and isoniazid to mice will cause accumulation of oxidative stress in the mitochondria in liver cells, resulting in damage and resulting in an imbalance in lipid metabolism and increased lipid markers such as LDL, cholesterol, and triglycerides, by giving papaya seed extract containing flavonoids to prevent the formation of oxidative stress and reduce levels of these biomarkers.

Papaya seeds contain quercetin [26]. According to a parametric study, routine oral administration of quercetin glycosides in streptozotocin-induced diabetic rats has been shown to reduce lipid levels in plasma and tissue. In particular, it was observed that normal increased plasma HDL cholesterol and lower LDL and VLDL cholesterol. Other types of flavonoids, such as Isoflavones, flavones, and flavanones, reduce blood cholesterol levels by inhibiting cholesterol synthesis and increasing the expression of LDL receptors. Soy isoflavones also affect plasma cholesterol levels through stimulation of LDL receptors. Dietary isoflavones, such as genistein or daidzein, induce plasma cholesterol reduction in C57BL / 6 mice but not in mice deficient in LDL receptors. Isoflavonoids such as formononetin, biochanin A, and daidzein increase LDL receptor activity in HepG2 cells [27].

4. CONCLUSION

In conclusions, ethanol extract of *caricayapapya* has a potential effect to prevent distruction of lipid metabolism effect by reducing the LDL, Triglycerides, Cholesterol Total, and increasing the level of HDL.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethics Commission from health and science commission, University Prima Indonesia (No.012/KEPK/UNPRI/III/2020). This research was conducted in Faculty of Pharmacy Universitas Sumatera Utara, March 2020 and the serum analyzed in Laboratory Kesehatan Daerah Sumatera Utara.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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