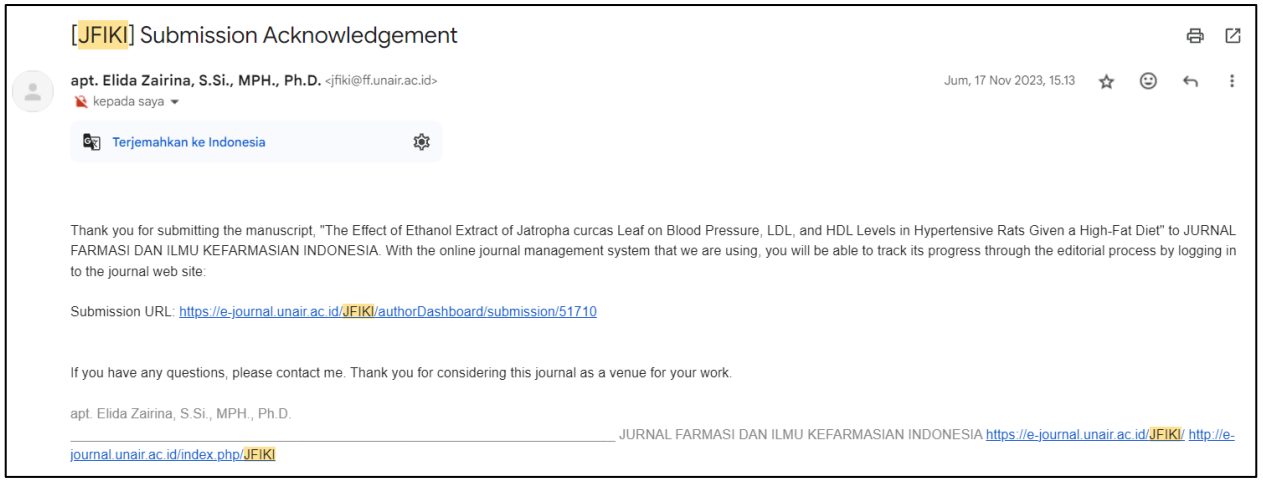
Daftar Isi

Lampiran 1. Informasi artikel berhasil di submit

Submit artikel ke Jurnal Farmasi dan Ilmu Kefarmasian Indonesia (JFIKI) dilakukan pada tanggal **17 November 2023**.



[JFIKI] Submission Acknowledgement

apt. Elida Zairina, S.Si., MPH., Ph.D. <jfiki@ff.unair.ac.id> Jum, 17 Nov 2023, 15.13

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Thank you for submitting the manuscript, "The Effect of Ethanol Extract of Jatropha curcas Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet" to JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

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If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

apt. Elida Zairina, S.Si., MPH., Ph.D.

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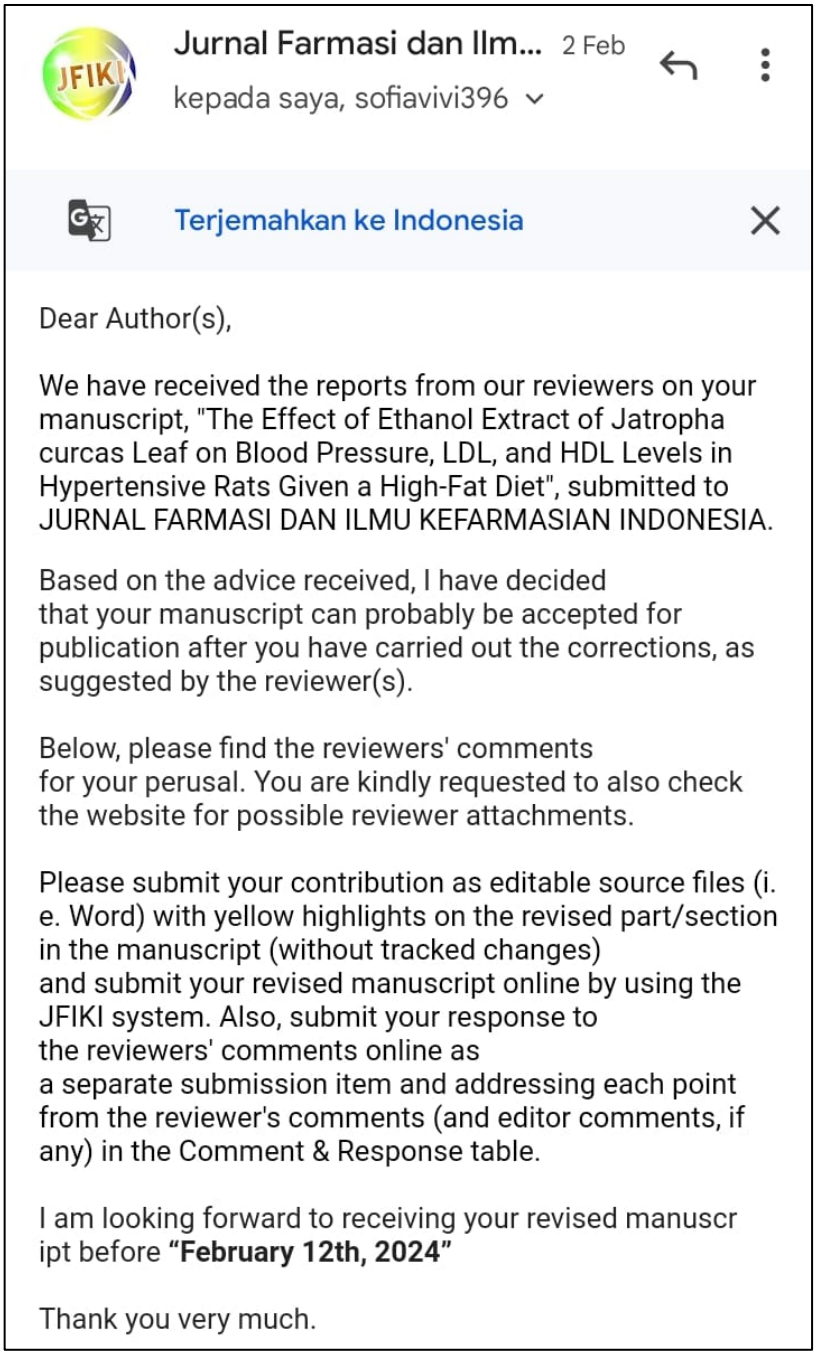
Lampiran 2. Informasi artikel mendapatkan revisi ke-1 dari reviewers

Artikel mendapat revisi ke-1 dari reviewers pada tanggal **2 Februari 2024.**



Jurnal Farmasi dan Ilm... 2 Feb

kepada saya, sofiavivi396

Terjemahkan ke Indonesia

Dear Author(s),

We have received the reports from our reviewers on your manuscript, "The Effect of Ethanol Extract of Jatropha curcas Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet", submitted to JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA.

Based on the advice received, I have decided that your manuscript can probably be accepted for publication after you have carried out the corrections, as suggested by the reviewer(s).

Below, please find the reviewers' comments for your perusal. You are kindly requested to also check the website for possible reviewer attachments.

Please submit your contribution as editable source files (i. e. Word) with yellow highlights on the revised part/section in the manuscript (without tracked changes) and submit your revised manuscript online by using the JFIKI system. Also, submit your response to the reviewers' comments online as a separate submission item and addressing each point from the reviewer's comments (and editor comments, if any) in the Comment & Response table.

I am looking forward to receiving your revised manuscr ipt before **"February 12th, 2024"**

Thank you very much.

REVIEWER I

JURNAL FARMASI DANILMU KEFARMASIAN INDONESIA (JFIKI)

Sekretariat : Faculty of Pharmacy, Universitas Airlangga (Kampus C),

Jl. Dr. Ir. H. Soekarno, Mulyorejo, Surabaya, Jawa Timur 60115e-mail:
jfiki@ff.unair.ac.id

REFEREE'S REPORT

Article ID :	51710
Title of Article :	The Effect of Ethanol Extract of Jatropha curcas Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diets

REVIEW

No.	Items	Very poor	Poor	Average	Good	Very Good
1	The manuscript contains original and self-consisted ideas and of interest	☐	☒	☐	☐	☐
2	The manuscript makes major contributions to the advancement of the subject	☐	☐	☒	☐	☐
3	The manuscript contains sufficient information included or cited to support the made assertions and the drawn conclusion	☐	☒	☐	☐	☐
4	The format of the manuscript (Tittle, Abstract, Introduction, Methods, Results and Discussion, Conclusion, Acknowledgements, References)	☐	☒	☐	☐	☐
5	The manuscript is clearly presented, well organized, and clearly written	☒	☐	☐	☐	☐
6	All the illustrations / figures and tables are adequate and necessary	☐	☒	☐	☐	☐
7	All the figures and tables' captions complete and accurate	☐	☒	☐	☐	☐
8	The references are adequate to related work, up to date and accessible	☐	☐	☒	☐	☐

Please give your appreciation of the scientific interest and novelty of results described

(in English)

REVIEW	
Title	-
Abstract	-
Introduction	It is necessary to improve the understanding of CAHD, dyslipidemia, and its relationship with LDL and HDL. If we trace the references used, it is possible that the author misunderstood what was written in them. The author could not provide a logical basis for the relationship between CAHD and hypertension and hypercholesterolemia. It would be better if the author used ethnomedicine data from Jatropha curcas as the basis for this research.
Methods	The terms used are unusual. Methods for determining compound groups, determining levels of compound groups is incomplete and unclear. Using 2 reference drugs as positive controls requires consideration and validation of the method so that it will guarantee the validity of the data got. Why not use two way anova?
Results and Discussion	The water content of the extract should be determined. In the section method there is no determination of the color and odor of the extract but there are results for determining the color and odor. The TLC image should be displayed, not just the Rf data. Is it true that the difference in total flavonoid and total phenolic levels is due to differences in external factors of the plant? What about the validity of the data? The author only provides a narrative of the results in the table, there is no discussion of the research results. What are the considerations for using the reference drug captopril for determining HDL and LDL and using the reference drug simvastatin for determining blood pressure?
Conclusion	-
References	It is essential for the author to understand the information written in the reference
Figures and Tables	What is the consideration of the mean diff and decrease percentage data in the table?
For article in English, is the English satisfactory? ☐ **YES** ☒**NO**	

REVIEWER II

The Effect of Ethanol Extract of *Jatropha curcas* Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet

Abstract

***Background**: One of the main risk factors for cardiovascular diseases such as Coronary atherosclerotic heart disease (CAHD) is dyslipidaemia or high levels of low-density lipoprotein (LDL) and triglycerides (TG) and low levels of high-density lipoprotein (HDL), hypertension is also a cause of cardiovascular disease. One potential plant to lower LDL levels and blood pressure is Jatropha curcas which is known to contain saponins, polyphenols, and flavonoids. **Objective**: The purpose of this study was to determine the effect of ethanol extract of Jatropha curcas leaf (EEJCL) on blood pressure, LDL, and HDL levels in hypertensive rats given a high-fat diet. **Methods**: This study was an experimental study with a pre-post test control group design on male Wistar strain rats. Rats were divided into 7 groups, namely the normalgroup, control (induced with NaCl and given a high-fat diet), Captopril, Simvastatin, EEJCL doses of 1.8 g/KgBW, 2.7 g/KgBW, and 4.05 g/KgBW. The data were analysed using the One-Sample Kolmogorov-Smirnov Test, Homogeneity ofVariances, One-Way ANOVA, and tukey tests. **Results**: The results showed that administration of EEJCL can significantly lower LDL levels and blood pressure ($p<0.050$) and increase HDL levels at all dose variations. **Conclusion**: EEJCL has potential for development in the treatment of hypertension and dyslipidaemia.*

***Keywords**: Cardiovascular, LDL, HDL, Blood pressure, Jatropha curcas*

INTRODUCTION

Cardiovascular diseases (CVDs), consisting of ischemic heart disease, stroke, heart failure, peripheral artery disease, and several other heart and blood vessel conditions, are the leading cause of global mortality and a major contributor to reduced quality of life. In 2017, CVDs caused around 17.8 million deaths worldwide, equivalent to 330 million years of life lost and 35.6 million more years lived with disability (Mensah et al., 2019).

Coronary atherosclerotic heart disease (CAHD) is dyslipidaemia or high levels of low-density lipoprotein (LDL) and triglycerides (TG) and low levels of high-density lipoprotein (HDL). High LDL can cause plaque formation and inflammatory cascades, progressing to atherosclerosis in the walls of arteries and thrombosis in CAHD. Meanwhile, HDL can strengthen tissues around artery walls, prevent cholesterol deposition in artery walls, and promote repair of damaged endothelial membranes. On the other hand, low HDL fails to remove cholesterol (Sun et al., 2022). Evaluation of the lipid profile (triglycerides, LDL cholesterol, HDL cholesterol and total cholesterol) in the blood is one way to identify the causes of hypertension, which is another cause of cardiovascular disease (Fuchs & Whelton, 2020). Research by Flint et al (2019) on the influence of systolic and diastolic blood pressure on cardiovascular explained that both systolic and diastolic blood pressure above the two threshold limits of ≥140/90 mm Hg and ≥130/80 mm Hg significantly contribute to cardiovascular disease risk (Flint et al., 2019).

The prescriber usually used for hypertension and dyslipidaemia are synthetic drugs such as captopril and simvastatin, but the use of herbal medicines is now developing and more preferred for long-term treatment due to their minimal side effects. One potential plant is *Jatropha curcas* which is known to contain saponins, polyphenols, and flavonoids that play a major role in treating various diseases, including bacterial and fungal infections as well as acting as antioxidants (Ait Babahmad et al., 2018). Research conducted by Anita et al (2023),reported that administration of ethanol extract of *Jatropha curcas* leaf can significantly reduce serum triglyceride levels at doses of 1.8 g/KgBW, 2.7 g/KgBW, 4.05 g/KgBW. Research results on physic nut leaf on HDL and LDL have also been reported by Anigbogu (2015), revealing that ethanol extract of *Jatropha curcas* leaf can increase HDL cholesterol concentration thereby reducing LDL cholesterol concentration. This indicates that ethanol extract of *Jatropha curcas* can be used for the treatment of cardiovascular disease. The purpose of this study was to further determine the effect of ethanol extract of *Jatropha curcas* leaf (EEJCL) on blood pressure, LDL, and HDL levels in hypertensive rats given a high-fat diet.

MATERIALS AND METHODS

This study is an experimental study with a pre-post test control group design and has obtained ethical approval from Ahmad Dahlan University with the number 011804052. The test animals were grouped into 7 groups, namely the normal group, negative control, Captopril, Simvastatin, and EEJCL 1.8; 2.7; and 4.05 g/kgBW. The test animals in groups other than normal were induced with 3.75 g/kgBW NaCl for 14 days to produce high blood pressure and a high-fat diet to produce hyperlipidaemia, while the normal group was only given standard feed.

Materials

The materials used in this study were *Jatropha curcas* L. leaves obtained from the Gunung Kidul area of Yogyakarta, 96% ethanol, Captopril, Simvastatin, NaCl, Na CMC, quercetin standard, gallic acid, Folin Ciocalteau reagent, $AlCl_3$, Na_2CO_3, Silica gel 60 F_{254}, methanol, ethyl acetate, chloroform. All chemicals used were Merck analytical grade. The test animals used were 35 male Wistar strain rats aged 2-3 months with weights of 200-250 grams.

Tools

The tools used included a drying cabinet, blender, glassware, an analytical balance, stirrer, macerator, vacuum, rotary evaporator, water bath, centrifuge, Eppendorf tubes, micropipettes, glassware, vortex, and UV- Vis spectrophotometer.

Methods

Production of Extract Ethanol of *Jatropha curcas* Leaf (EEJCL)

As much as 1700 grams of dried *Jatropha curcas* leaf powder was macerated using 96% ethanol as a solvent in a ratio of 1: 4, stirred for 3 hours and left to stand for 24 hours. Extraction was carried out 3 times. The extracts were evaporated using a rotary evaporator at 70°C and water bath until a thick extract was obtained (Anita & Bachri, 2023).

Compound Identification using TLC

Thin layer chromatography was carried out with silica gel F_{254} solid phase and mobile phase of hexane: ethyl acetate: formic acid (6:4:0.2) for flavonoid analysis and mobile phase HCl_3: MeOH: H_2O (7:3.5: 1). Sample spots

were sprayed with $FeCl_3$ reagent for polyphenols and ammonia vapor for flavonoids and then compared to standard compound spots, and the Rf value of each sample was determined (Saepudin et al., 2023).

Total Flavonoid test

As much as 10 mg ethanol extract of *Jatropha curcas* leaf was dissolved in 10 ml of ethanol p.a and 1 ml was pipetted out of 5 ml. The resulting solution was pipetted 2 ml and added with 2 ml of 2% AlCl3. Absorbance was read with a spectrophotometer at a wavelength of 510 nm. Quercetin standard was prepared by dissolving quercetin in ethanol p.a and made at concentrations of 4, 6, 8, 10, 12 µg/ml. The samples were examined with three replications. The flavonoid content was expressed as equivalent to quercetin (Endah, 2016).

Total Phenolic Test

As much as 10 mg of ethanol extract of *Jatropha curcas* leaves was dissolved in 10 ml of p.a ethanol as solvent and then pipetted 1 ml to 5 ml. The obtained solution was pipetted 300 µl and added 1.5 ml Folin-Ciocalteu reagent. After being left for 3 minutes, 1.2 ml of 7.5% Na_2CO_3 solution was added and left again at room temperature. Absorbance was read with a spectrophotometer at a wavelength of 750 nm. Gallic acid standard solutions were made in concentrations of 15, 20, 25, 30, 35 µg/ml each put into tubes, then added 1.5 ml Folin-Ciocalteu reagent (1:10), then a calibration curve was made of the relationship between gallic acid concentration (µg/ml) and absorbance (Endah, 2016).

Antihypertensive Activity Test

The induced test animals, on day 15 until day 21 in the control animal group were given CMC-Na treatment, the Captopril group was given a Captopril suspension at a dose of 4.5 mg/KgBW, the Simvastatin group was given a Simvastatin suspension at a dose of 0.9 mg/KgBW, and the extract group was given EEJCL 1.8; 2.7; and 4.05 g/KgBW. Blood pressure measurements were carried out on day 14 for pre-treatment data. Then the test sample administration was carried out from day 15 to day 21, during this time span blood pressure measurements were carried out on day 17, 20, and day 22.

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LDL Test

The induced test animals in the normal and negative groups were given treatment with NaCMC, the positive group was given Captopril 4.5 mg/kgBW, the second positive group was given Simvastatin 0.9 mg/kgBW, and dose groups 1, 2, and 3 were given ethanol extracts of *Jatropha curcas* leaves (EEJCL) namely 1.8; 2.7; and 4.05 mg/kgBW respectively. Blood sampling was carried out twice, before and after treatment, by fasting the rats for ± 12 hours. Blood sampling of 3 mL was carried out through the retro-orbital sinus after being anesthetized with ether (Nurmeilis, 2015). The blood was then centrifuged to obtain the serum. The data analysis was in the form of LDL cholesterol levels data on hypertensive Wistar rats given a high-fat diet. Determination of LDL cholesterol levels used the enzymatic colorimetric test method to directly measure LDL cholesterol levels.

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HDL Test

The induced test animals from day 15 to day 21 in the control animal group were given CMC-Na treatment, the Captopril group was given a Captopril suspension at a dose of 4.5 mg/KgBW, the Simvastatin group was given a Simvastatin suspension at a dose of 0.9 mg/KgBW, and the extract group was given EEJCL 1.8; 2.7; and 4.05 g/KgBW. Blood sampling was done twice, before and after treatment, on day 15 and day 22. The obtained blood was separated between serum and plasma. The serum was then prepared with CHOD-PAP reagent and read on a uv-vis spectrophotometer with a wavelength of 546 nm. Calculations were made on the obtained data to obtain HDL levels in blood.

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Data Analysis

The data analysis was conducted using SPSS with preliminary tests including the Kolmogorov-Smirnov test to determine if the data was normally distributed or not, and the Levene test to determine if the variance was homogeneous or not. If the obtained data was normally distributed ($p>0.05$) and homogeneous ($p>0.05$), then it was continued with the parametric one-way ANOVA at a 95% confidence level. The analysis was further continued with a post hoc test used tukey test to show significant differences between treatment groups.

RESULTS AND DISCUSSION

Extraction of *Jatropha curcas* leaves

Extraction of dried powder from *Jatropha curcas* leaves yielded a thick extract of 84.7 g from a total of 1.7 kg of dried powder with a yield of 4.98%, green in color and aromatic in smell.

Compounds contained in *Jatropha curcas* leaves through TLC testing

The results of thin layer chromatography testing after being passed under ammonia vapor under visible light, indicating the presence of flavonoid compounds with Rf 0,50. Then after spraying with $FeCl_3$, the contained phenolic compounds will appear. The results indicate that the ethanol extract of *Jatropha curcas* leaves contains phenolic compounds with Rf 0,18.

Testing of total flavonoid and total phenolic content

The results of the total flavonoid content test were 4.41% ± 0.04 and total phenolics were 11.03% ± 0.60. The obtained values were above the total phenol and flavonoid previously studied by Sadik et al (2017) with total flavonoids of 1.48% ± 0.01 and total phenolics of 5.51% ± 0.01. The results obtained differed, possibly due to differences in environmental conditions such as temperature, soil, and plant cultivation processes.

Antihypertensive testing

The study was conducted on 7 groups of test animals each consisting of 5 rats. Blood pressure measurement averages were conducted on day 14, day 17, day 20, and day 22. The results obtained from each measurement can be seen in Tables 1, 2 and 3.

Table 1. Systolic blood pressure measurement results on day 14, day 17, day 20, and day 22

Groups	Dose (g/KgBW)	Average of Systolic blood pressure (mmHg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	119,0±6,51	123,0±9,13	117,0±5,56	120,0±8,24
Control	-	151,0±7,74	145,8±2,77	155,8± 6,91	137,4±5,40
Captopril	0,0045	148,6 ±12,4	122,8±3,19*	118,0±5,65*	121,4±9,55*
Simvastatin	0,0009	146,4±10,45	135,4±9,75	121,2±9,03*	127,0±6,24*
EEJCL	1,8	143,2±3,96	126,2±10,98	126,4±12,19*	114,8±9.75*
	2,7	143,8±11,88	141,0±13,43	129,8±18,55*	113,4±8,26*
	4,05	139,6±6,18	130,2±17,15*	127,0±16,53*	118,0±8,71*

*)p<0,05 significantly different from the control group

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The data of systolic blood pressure measurement (Table 1), it was found that the administration of ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower systolic blood pressure in the blood, where the most effective EEJCL dose in this test was 2.7 g/kgBW, namely a decrease greater than the comparative group (captopril). Previous studies Sadik et al (2021) also found that plants containing flavonoid compounds can lower blood pressure. The results of one-way ANOVA statistical tests on systolic blood pressure obtained a significant value ($p<0.05$), meaning there was an effect of decreasing systolic blood pressure after being given test preparations, so it can be concluded that there is effectiveness of administering ethanol extract of *Jatropha curcas* leaves (EEJCL) as an antihypertensive on male Wistar strain rats.

Table 2. Diastolic blood pressure measurement results on day 14, day 17, day 20, and day 22

Groups	Dosis (g/KgBW)	Average of Diastolic blood pressure (mmHg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	84,8±5,89*	76,6±12,01*	76,8±11,73*	73,0±5,52*
Control	-	115,4±7,19	116,2±20,48	114,8±16,33	92,8±6,30
Captopril	0,0045	100,4±26,85	99,0±14,91	90,6±12,3*	91,8±20,5*
Simvastatin	0,0009	90,0±12,44*	89,8±20,6*	94,6±8,96*	85,6±10,1
EEJCL	1,8	111,8±6,05	99,6±12,15	91,8±15,62*	78,0±7,71*
	2,7	109,0±10,29	102,0±12,58	95,0±16,077*	77,6±12,46*
	4,05	112,2±9,36	94,4±18,82*	90,0±17,91*	81,8±13,14*

*)p<0,05 significantly different from the control group

Commented [R5]: Same suggestion.

The diastolic blood pressure measurement data (Table 2), it was found that the administration of ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower diastolic blood pressure in the blood, where the most effective EEJCL dose in this test was 2.7 g/kgBW, namely a decrease greater than the comparative group (captopril). Previous studies Sadik et al (2021) also found that plants containing flavonoid compounds can lower blood pressure. The results of one-way ANOVA statistical tests on diastolic blood pressure obtained a significant value ($p<0.05$), meaning there was an effect of decreasing diastolic blood pressure after being given test preparations, so it can be concluded that there is effectiveness of administering ethanol extract of *Jatropha curcas* leaves (EEJCL) as an antihypertensive on male Wistar strain rats.

Table 3. Mean arterial blood pressure measurement results on day 14, day 17, day 20, and day 22

Groups	Dose (g/KgBW)	Mean arterial blood pressure (mmHg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	98,0±8,97	92,6±7,40	94,4±5,17	88,4±6,02
Control	-	127,8±6,26	108,4±12,3	128,2±16,55	110,8±14,75
Captopril	0,0045	123,4±10,23	129±19,27*	98,8±8,40*	93,8 ± 6,64*
Simvastatin	0,0009	121,4±8,87	120,2±7,46	103,6±7,40*	100,0 ±3,74
EEJCL	1,8	119±5,47	115,6±18,35	103,6±15,37*	89,8±7,56*
	2,7	118,6±10,33	113,2±10,35	106,4±16,63*	90,0±11,37*
	4,05	117,8±10,32	98,0±19,91*	105,2±13,4*	90,6±9,76*

*)p<0,05 significantly different from the control group

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The mean arterial blood pressure measurement data (Table 3), it was found that the administration of ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower the mean arterial blood pressure in the blood, where the most effective EEJCL dose in this test was 1.8 g/kgBW, namely a decrease greater than the comparative group (captopril). Blood pressure measurements on day 20 and day 22 had already shown a significant decrease in blood pressure approaching normal. Statistical test results showed a significant difference between dose groups and induction groups, while statistical results of dose groups compared to normal and captopril groups showed no significant difference. In *Jatropha curcas* leaf ethanol extract, flavonoids have ACE inhibitory activity, this

activity is due to the formation of chelate complexes at the ACE active centre, and depends on the main structural features of flavonoids. Therefore, the flavonoid content in extracts and proven antioxidant activity support the ability as an antihypertensive (Dhianawaty et al., 2018). Thus, in the EEJCL 1.8; EEJCL 2.7; and EEJCL 4.05 groups, blood pressure in test rats could be lowered to approach normal.

LDL Testing

LDL level measurement studies were conducted on 7 animal test groups, each consisting of 5 rats. The LDL level measurement results on day 15 and day 22 in each group can be seen in Table 4.

Table 4. LDL level measurement results (mg/dL) after being given Captopril, Simvastatin, and Ethanol Extract of *Jatropha curcas* Leaves (EEJCL)

Groups	Dose (g/KgBW)	Day-15[1)] (Mean ± SD)	Day-22[2)] (Mean ± SD)	Difference (Mean ± SD)	Decrease percentage (%)
Normal	-	24,25 ± 2,41	22,92 ± 4.648	1,33 ± 3,79[*]	5
Control	-	36,64 ± 1,58	48,56 ± 3.012	-11,91 ± 4,01	-32
Captopril	0,0045	36,75 ± 0,95	37,94 ± 1.893	-1,21 ± 1,56[*]	-3
Simvastatin	0,0009	42,74 ± 1,64	24,70 ± 1.891	18,04 ± 2,91[*]	42
EEJCL	1,8	37,82 ± 4,97	27,57 ± 3.909	10,24 ± 5,25[*]	27
	2,7	38,53 ± 2,87	26,16 ± 1.943	12,37 ± 4,02[*]	32
	4,05	38,47 ± 1,97	24,15 ± 1.221	14,31 ± 1,48[*]	37

[*)]p<0,05 significantly different from the control group
[1)] Day 15 after being given high fat feed and given NaCl 3.75 g/KgBW for 14 days
[2)] Day 22 after being given ethanol extract of *Jatropha curcas* leaves (EEJCL) for 7 days

The statistical test results of the EEJCL 1.8; EEJCL 2.7; and EEJCL 4.05 groups showed a significant difference (p <0.05) compared to the control group. The Captopril and Simvastatin groups were significantly different with a value (p <0.05) compared to the control group. The EEJCL 1.8 and EEJCL 4.05 groups showed no significant difference with a value (p> 0.05) compared to the Simvastatin group. The EEJCL 2.7 group showed a significant difference (p <0.05) compared to the Simvastatin group. This shows that the administration of EEJCL can lower LDL levels but has not reached normal levels. The data results of the difference in rat LDL levels can be seen in Table 4.

The decrease in blood pressure and LDL is related to the presence of flavonoid compounds. Various studies have proven that flavonoid content can lower blood pressure and LDL by inhibiting angiotensin converting enzyme and binding free radicals and metal ion transitions in inhibiting lipid peroxidation (Loh et al., 2020). Flavonoids have the ability to stop oxidative damage and LDL oxidation. In addition, luteolin derivatives can trigger cholesterol barrier secretion, meaning cholesterol levels decrease. When cholesterol is transported from the intestine to the liver, flavonoids function as inhibitors of the HMGCoA reductase enzyme, the enzyme responsible for converting acetyl-CoA to mevalonate in cholesterol synthesis, thus reducing synthesis (Nuralifah et al., 2020). Thus, the administration of ethanol extract of *Jatropha curcas* leaves (EEJCL) for 7 days can lower LDL levels in hypertensive rats given a high-fat diet.

HDL Testing

The study of LDL level measurements was conducted on 7 animal test groups, each consisting of 5 rats. The results of HDL measurements on day 15 and day 22 in each group can be seen in Table 5.

Table 5. HDL level measurement results (mg/dL) after being given Captopril, Simvastatin, and Ethanol Extract of *Jatropha curcas* Leaves (EEJCL)

Groups	Dose (g/KgBW)	Day15[1)] (Mean ± SD)	Day-22[2)] (Mean ± SD)	Difference (Mean ± SD)	Decrease percentage (%)
Normal	-	34,57 ± 1,17	36,67 ± 0,78	2,09 ± 1,63[a]	5
Control	-	23,39 ± 1,89	26,40 ± 2,38	3,01 ± 2,23[a]	11
Captopril	0,0045	24,29 ± 2,41	25,83 ± 1,56	1,53 ± 1,25[a]	5
Simvastatin	0,0009	24,61 ± 1,21	33,82 ± 0,57	9,18 ± 1,12[b]	27
EEJCL	1,8	24,58 ± 2,35	27,45 ± 1,49	2,87 ± 1,56[a]	10
	2,7	24,58 ± 3,29	29,64 ± 1,49	5,05 ± 2,95[a]	17
	4,05	23,46 ± 2,86	35,60 ± 0,67	12,14 ± 2,32[a,b]	34

[a)]p<0,05, significantly different from the simvastatin
[b)]p<0,05, significantly different from the control group
[1)] Day 15 after being given high fat feed and given NaCl 3.75 g/KgBW for 14 days
[2)] Day 22 after being given ethanol extract of *Jatropha curacas* leaves (EEJCL) for 7 days

Commented [R7]: Same suggestion.

Commented [R8]: Same suggestion.

The control group; Captopril; Simvastatin; EEJCL 1.8; EEJCL 2.7; and EEJCL 4.05 groups before treatment had lower HDL levels compared to the normal group (Table 5). This is because groups other than normal were given a high-fat diet containing a lot of cholesterol. HDL is said to be low if the level is <30 mg/dL (Hernáez et al., 2019). Then the HDL levels in each group showed an increase after EEJCL administration. Table 4 shows that there was an increase in HDL levels after being given EEJCL treatment in each group. This shows that *Jatropha curcas* leaf ethanol extract is able to increase HDL levels. Consistent with previous research conducted by Anigbogu et al (2015) that *Jatropha curcas* leaf ethanol extract can increase HDL levels. The increase in HDL levels occurred after administration of ethanol extract of *Jatropha curcas* leaves which was known to contain flavonoid compounds.

In this study, the highest HDL level increase occurred in the EEJCL 4.05 group. With increasing drug doses, the effects given should provide comparable effects with increased doses. Ultimately, with increasing doses, the effects will decrease. This is because the dose can no longer maximally provide effects. This case often occurs in traditional or herbal medicines where the content is no longer a single chemical compound but several types of chemical compounds that work together to provide effects. It is not impossible that with increasing doses, the amount of contained compounds also increases and unwanted reactions occur that can reduce effects (Siskayanti et al., 2017).

The same study was also conducted by Abdulmumin (2020), reporting that extracts of *Jatropha Curcas* leaves, peel, stems and roots have hypolipidemic activity and may be useful in managing cardiovascular disease. While the acute toxicity (LD50) of *Jatropha curcas* leaf, peel, stem and root extracts was greater than 5000 mg/kg, thus declared practically non-toxic to experimental animals (Mika'il et al., 2020). Administering treatments such as EEJCL containing flavonoids is likely to increase endothelial nitric oxide (eNOS) synthesis, thus increasing NO bioavailability. Flavonoids can act as vasodilators with suitable signaling pathways and structural characteristics for strong vasorelaxant properties (Loh et al., 2020). Therefore, ethanol extract of *Jatropha curcas* leaf has potential for development in the treatment of hypertension and dyslipidaemia, so this study will be a reference for further similar topic research in the future and has the potential to lead to the development of more promising antihypertensive alternatives.

Commented [R9]: Did they extracted in the similar method?

Commented [R10]: Is there any data on cholesterol levels?

CONCLUSION

Jatropha curcas leaves have potential in lowering blood preassure, LDL, and increasing HDL levels. The ethanol extract of *Jatropha curcas* leaves (EEJCL) has potential for development in the treatment of hypertension and dyslipidaemia

ACKNOWLEDGEMENT

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JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA (JFIKI)
Sekretariat : Faculty of Pharmacy, Universitas Airlangga (Kampus C),

Jl. Dr. Ir. H. Soekarno, Mulyorejo, Surabaya, Jawa Timur 60115
e-mail: jfiki@ff.unair.ac.id

REFEREE'S REPORT

Article ID :	51710
Title of Article :	The Effect of Ethanol Extract of Jatropha curcas Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diets

REVIEW

No.	Items	Very poor	Poor	Average	Good	Very Good
1	The manuscript contains original and self-consisted ideas and of interest	☐	☐	☒	☐	☐
2	The manuscript makes major contributions to the advancement of the subject	☐	☐	☒	☐	☐
3	The manuscript contains sufficient information included or cited to support the made assertions and the drawn conclusion	☐	☐	☒	☐	☐
4	The format of the manuscript (Tittle, Abstract, Introduction, Methods, Results and Discussion, Conclusion, Acknowledgements, References)	☐	☐	☒	☐	☐
5	The manuscript is clearly presented, well organized, and clearly written	☐	☐	☒	☐	☐
6	All the illustrations / figures and tables are adequate and necessary	☐	☐	☒	☐	☐
7	All the figures and tables' captions complete and accurate	☐	☒	☐	☐	☐
8	The references are adequate to related work, up to date and accessible	☐	☐	☒	☐	☐

Please give your appreciation of the scientific interest and novelty of results described

(in English)

REVIEW	
Title	Fine
Abstract	Need revision.
Introduction	Fine
Methods	Need some revision.
Results and Discussion	Need some revision on table and discussion further.
Conclusion	Fine
References	Fine
Figures and Tables	Need some revision.
For article in English, is the English satisfactory? ☒**YES** ☐**NO**	

REVIEWER III

JURNAL FARMASI DANILMU KEFARMASIAN INDONESIA (JFIKI)
Sekretariat : Faculty of Pharmacy, Universitas Airlangga (Kampus C),
Jl. Dr. Ir. H. Soekarno, Mulyorejo, Surabaya, Jawa Timur 60115
e-mail: jfiki@ff.unair.ac.id

REFEREE'S REPORT

51710

Article ID :	
Title of Article :	**The Effect of Ethanol Extract of *Jatropha curcas* Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet**

REVIEW

No.	Items	Very poor	Poor	Average	Good	Very Good
1	The manuscript contains original and self-consisted ideas and of interest	☐	☐	☒	☐	☐
2	The manuscript makes major contributions to the advancement of the subject	☐	☐	☒	☐	☐
3	The manuscript contains sufficient information included or cited to support the made assertions and the drawn conclusion	☐	☐	☐	☒	☐
4	The format of the manuscript (Tittle, Abstract, Introduction, Methods, Results and Discussion, Conclusion, Acknowledgements, References)	☐	☐	☐	☒	☐
5	The manuscript is clearly presented, well organized, and clearly written	☐	☐	☒	☐	☐
6	All the illustrations / figures and tables are adequate and necessary	☐	☐	☒	☐	☐
7	All the figures and tables' captions complete and accurate	☐	☐	☒	☐	☐
8	The references are adequate to related work, up to date and accessible	☐	☐	☒	☐	☐

Please give your *appreciation of the scientific interest and novelty* of results described
(in English)

REVIEW	
Title	Nama latin tanaman kurang lengkap harusnya ada Author
Abstract	The results showed that administration of EEJCL can significantly lower LDL levels and blood pressure ($p<0.050$) and increase HDL levels at all dose variations. Masih kurang lengkap : sebaiknya disebutkan berapa persen penurunan tekanan darah dan Peningkatan HDL nya
Introduction	Perlu ada informasi apakah ekstrak Jatropa juga pernah diuji aktivitas tekanan darah dari pustaka atau data empirisnya?
Methods	1. Determinasi tanaman apakah sudah dilakukan? Untuk memastikan sampel yang diambil adalah benar 2. Kenapa digunakan dosis teralu tinggi : EEJCL 1.8; 2.7; and 4.05 g/kgBW ? karena kalau ini nanti akan dikembangkan menajdi sediaan OHT dosis konversinya ke manusia tentu tidak eligible? Alasan apa ? 3. Production of Extract Ethanol of Jatropha curcas Leaf (EEJCL) ; apada standarisasinya ? minimal kadar air berapa? 4. **The induced test animals** cara bagaimana tidak dijelaskan? Evaluasinya seperti apa kalau hewan coba sudah hipertensi? Dan tidak tahapan aklimatisasi hewan coba dan perlakuan sebagaimana protokoluji preklinik yang baik 5. Compounds contained in Jatropha curcas leaves through TLC testing : Hasil TLC perlu ditampilkan dan pembanding apa ? kenapa bisa menyimpulkan Rf 0,5 adalah flavonoid dan 0,18 phenol dasarnya apa ? 6. The results of the total flavonoid content test were 4.41% ± 0.04 and total phenolics were 11.03% ± 0.60 : apa benar metode yang digunakan ? Berapa harga R regresinya ? kalaun bisa dicantumkan karena menurut reviewer terlalu tinggi- apa ada pembanding penelitia sejenis mengenai kuantifikasi kadar flavonoid dan phenol dari ekstrak Jarak ini??
Results and Discussion	1. Compounds contained in Jatropha curcas leaves through TLC testing : Hasil TLC perlu ditampilkan dan pembanding apa ? kenapa bisa menyimpulkan Rf 0,5 adalah flavonoid dan 0,18 phenol dasarnya apa ? 2.The results of the total flavonoid content test were 4.41% ± 0.04 and total phenolics were 11.03% ± 0.60 : apa benar metode yang digunakan ? Berapa harga R regresinya ? kalaun bisa dicantumkan karena menurut reviewer terlalu tinggi- apa ada pembanding penelitia sejenis mengenai kuantifikasi kadar flavonoid dan phenol dari ekstrak Jarak ini?? 3. Kenapa pada hasil LDL level measurement results (mg/dL) after being given Captopril, Simvastatin, and Ethanol Extract of Jatropha curcas Leaves (EEJCL) ada hasil yang minus – mohon dijelaskan?
Conclusion	Kurang jelas dan informatif dari hasil penelitian yang sangat banyak parameter yang diukur ?
References	Ok
Figures and Tables	Gambar TLC belum ada dan akalunperlu ditampilkan kurva regresi PK flavonoid dan Phenol
For article in English, is the English satisfactory?	yes

Lampiran 3. Informasi pengiriman hasil revisi ke-1 ke reviewers

Artikel kembali dikirimkan hasil revisi ke-1 ke reviewers pada tanggal **11 Februari 2024**

COMMENT AND RESPONSE

REVIEWER 1

Comments	Responses	Page
It is necessary to improve the understanding of CAHD, dyslipidemia, and its relationship with LDL and HDL. If we trace the references used, it is possible that the author misunderstood what was written in them.	Thank you for the review you have given us. We have revised that section	In Page 1 lines 36-41
The author could not provide a logical basis for the relationship between CAHD and hypertension and hypercholesterolemia. It would be better if the author used ethnomedicine data from Jatropha curcas as the basis for this research.	Thank you for the review you have given us. We have revised that section	In Page 2 lines 58-60
Methods for determining compound groups, determining levels of compound groups is incomplete and unclear	Thank you for the review you have given us. We have revised that section	In Page 2 lines 89 and 95
Using 2 reference drugs as positive controls requires consideration and validation of the method so that it will guarantee the validity of the data got.	Thank you for the review you have given us. We wanted to know which rats had hypertension and hypercholesterolemia, so we used 2 positive controls	
Why not use two way anova?	Thank you for the review you have given us. In this study there were 2 variables for the day and blood pressure, LDL levels, and HDL levels. However, we want to carry out an analysis between days per result so we use the one way ANOVA test	
The TLC image should be displayed, not just the Rf data	Thank you for the review you have given us. We have added image TLC to our article	In Page 3 lines 160 and 184
Is it true that the difference in total flavonoid and total phenolic levels is due to differences in external factors of	Thank you for the review you have given us. The differences in content are caused by the location of the plant samples taken. So the	

the plant? What about the validity of the data?	levels of flavonoids and phenolics obtained are also different and the data analysis method for these levels is using UV-Vis spectrophotometry.	
The author only provides a narrative of the results in the table, there is no discussion of the research results.	Thank you for the review you have given us. We have improved our discussion by adding a few references to the results and discussion	
What are the considerations for using the reference drug captopril for determining HDL and LDL and using the reference drug simvastatin for determining blood pressure?	Thank you for the review you have given us. Yes, this must be revised regarding drug references for hypertension only, while simvastatin is for LDL and HDL levels	
It is essential for the author to understand the information written in the reference	Thank you for the review you have given us. We have revised the bibliography to comply with the rules of the JFIKI journal	
What is the consideration of the mean diff and decrease percentage data in the table?	Thank you for the review you have given us. The data on percentages that we present in the table are percentage decreases calculated using the formula: Persentage of decreased (%)= $\frac{[(\text{Day-15}) - (\text{Day-22})]}{(\text{Day-15})}$ x 100% Meanwhile, the difference data is the difference data between each treatment group in the experimental animals	

REVIEWER 2

Comments	Responses	Page
Remove this treatment	Thank you for the comments that have been given, we have deleted them and corrected them according to the input given in the method section	In Page 2 and 3 lines 102, 111, and 119
It is not an appropriate treatment if the researcher want to see systolic, diastolic, and mean arterial blood pressure. Remove this results.	Thank you for the comments that have been given, we have removed them and corrected the blood measurement table section	In Table 5, 6, and 7
It is not an appropriate treatment if the researcher want to see LDL Level and HDL Level. Remove this results	Thank you for the comments that have been given, we have removed them and corrected the LDL and HDL measurement table section	In Table 8 and 9
Did they extracted in the similar method?	Thank you for the comments given to us, the extraction method used is the same	
Is there any data on cholesterol levels?	Thank you for the comments given to us, the data on cholesterol levels in rats In *R. norvegicus* Wistar strain rats, the normal blood cholesterol level is 10-54 mg/dl.	

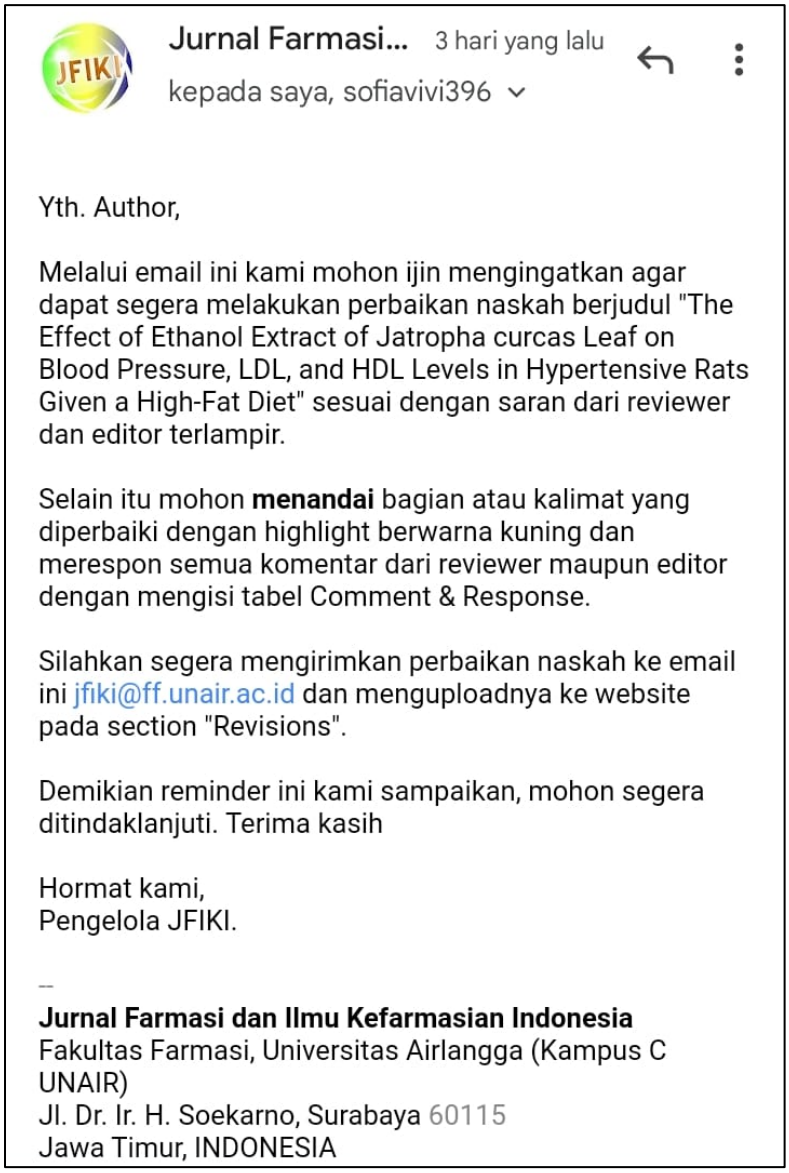
REVIEWER 3

Comments	Responses	Page
Nama latin tanaman kurang lengkap	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah melengkapi nama latin yang benar.	
The results showed that administration of EEJCL can significantly lower LDL levels and blood pressure ($p<0.050$) and increase HDL levels at all dose variations. Masih kurang lengkap: sebaiknya disebutkan berapa persen penurunan tekanan darahnya dan peningkatan HDL nya.	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah merevisi bagian tersebut pada bagian abstrak	Page 1, lines 24-26.
Perlu ada informasi apakah ekstrak Jatropa pernah diuji aktivitas tekanan darah dari pustaka atau data empirisnya.	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah menambahkan pustaka mengenai penelitian terdahulu pada bagian pendahuluan	Page 1, lines 51-52
Determinasi tanaman apakah sudah sudah dilakukan ?. Untuk meemastikan sampel yang diambil adalah benar	Terima kasih atas masukkan yang diberikan kepada kami. Sampel kami telah dilakukan determinasi dan kami telah menambahkan keterangan determinasi tersebut pada bagian metode	Page 2, lines 69-71
Kenapa digunakan dosis terlalu tinggi : EEJCL 1.8; 2.7; dan 4.05 g/KgBB ? karena kalau ini nanti akan dikembangkan sediaan OHT dosis konversinya ke manusia tentu tidak eligible ? Alasan apa ?	Terima kasih atas masukkan yang diberikan kepada kami. Penggunaan dosis tersebut telah didasari oleh penelitian terdahulu oleh Sadik (2021), dan masih diperlukan penelitian lanjut untuk mendapatkan dosis ekstrak atau fraksi yang lebih kecil yang rasional untuk dikonversi dan digunakan oleh manusia	
Production of Extract Ethanol of *Jatropha curcas* Leaf (EEJCL); apa standarisasinya ? minimal kadar air berapa ?	Terima kasih atas masukkan yang diberikan kepada kami. Untuk pengukuran kadar air kami belum melakukannya, dengan itu masih perlu dilakukan penelitian-penelitian lanjutan di waktu yang akan datang.	
The induced test animals, cara bagaimana tidak dijelaskan ? Evaluasinya seperti apa kalau hewan coba sudah hipertensi? Dan tidak tahapan aklimatisasi hewan coba dan perlakuan sebagaimana protokol uji preklinik yang baik	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah menambahkan masukan tersebut pada bagian metode di halaman 2, baris ke 102.	Page 2, lines 102
Compounds contained in Jatropha curcas leaves through TLC testing : Hasil TLC perlu ditampilkan dan	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah menambahkan pembahasan ini pada	Page 3 dan 4,

pembanding apa ? kenapa bisa menyimpulkan Rf 0,5 adalah flavonoid dan 0,18 phenol dasarnya apa?	bagian pembahasan di halaman 3 dan 4, baris 160 dan 184**.**	lines 160 dan 184
Kenapa pada hasil LDL level measurement result (mg/dl) after being given Captropil, simvastatin, and ethanol extract of Jatropha curcas leaves (EEJCL) ada hasil minus (-) mohon dijelaskan ?	Terima kasih atas masukkan yang diberikan kepada kami. Dikarenakan pada kelompok kontrol yang hanya diberi NaCMC dan dijadikan pembanding setelah diberi perlakuan maka kadar LDL nya tidak mengalami penurunan.	
Kurang jelas dan informatif dari hasil penelitian yang sangat banyak parameter yang diukur ?	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah merevisi pada bagian kesimpulan yang telah menjelaskan hasil dari penelitian ini	Page 7, lines 318
Gambar TLC belum ada dan kalau perlu ditampilkan kurva regresi pengukuran kadar flavonoid dan phenol	Terima kasih atas masukkan yang diberikan kepada kami. Kami telah menambahkan pembahasan ini pada bagian pembahasan tentang gambar TLC di halaman 3 dan 4, baris 160 dan 184 serta kurva regresi	Page 4 dan 5, lines 195 dan 206

Lampiran 4. Informasi artikel mendapatkan revisi ke-2 dari reviewers

Artikel mendapat revisi ke-2 dari reviewers pada tanggal **8 Maret 2024**



Jurnal Farmasi... 3 hari yang lalu

kepada saya, sofiavivi396

Yth. Author,

Melalui email ini kami mohon ijin mengingatkan agar dapat segera melakukan perbaikan naskah berjudul "The Effect of Ethanol Extract of Jatropha curcas Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet" sesuai dengan saran dari reviewer dan editor terlampir.

Selain itu mohon **menandai** bagian atau kalimat yang diperbaiki dengan highlight berwarna kuning dan merespon semua komentar dari reviewer maupun editor dengan mengisi tabel Comment & Response.

Silahkan segera mengirimkan perbaikan naskah ke email ini jfiki@ff.unair.ac.id dan menguploadnya ke website pada section "Revisions".

Demikian reminder ini kami sampaikan, mohon segera ditindaklanjuti. Terima kasih

Hormat kami,
Pengelola JFIKI.

--
Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Fakultas Farmasi, Universitas Airlangga (Kampus C UNAIR)
Jl. Dr. Ir. H. Soekarno, Surabaya 60115
Jawa Timur, INDONESIA

The Effect of Ethanol Extract of *Jatropha curcas* L. Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet

Moch Saiful Bachri[1*], Wiki Yuli Anita[1], Putri Dwi Lestari[1], Desi Eko Wulansari[1], Dwi Retno Nengtyas[1], Muhammad Ma'ruf[1], Sapto Yuliani[1], Wahyu Widyaningsih[1], Laela Hayu Nurani[1], Daru Estiningsih[2], Vivi Sofia[3]

[1]Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia
[2]Laboratory Pharmacology, Laboratory Pharmacology, Faculty of Health Sciences, Alma Ata University, Yogyakarta, Indonesia
[3]Faculty of Pharmacy, Tjut Nyak Dien University, North Sumatra, Indonesia

[*]Corresponding author: msaifulbachri@pharm.uad.ac.id

Abstract

***Background**: One of the main risk factors for cardiovascular diseases such as Coronary atherosclerotic heart disease (CAHD) is dyslipidaemia or high levels of low-density lipoprotein (LDL) and triglycerides (TG) and low levels of high-density lipoprotein (HDL), hypertension is also a cause of cardiovascular disease. One potential plant to lower LDL levels and blood pressure is Jatropha curcas which is known to contain saponins, polyphenols, and flavonoids. **Objective**: The purpose of this study was to determine the effect of ethanol extract of Jatropha curcas leaf (EEJCL) on blood pressure, LDL, and HDL levels in hypertensive rats given a high-fat diet. **Methods**: This study was an experimental study with a pre-post test control group design on male Wistar strain rats. Rats were divided into 7 groups, namely the normal group, control (induced with NaCl and given a high-fat diet), Captopril, Simvastatin, EEJCL doses of 1.8 g/KgBW, 2.7 g/KgBW, and 4.05 g/KgBW. The data were analysed using the One-Sample Kolmogorov-Smirnov Test, Homogeneity of Variances, One-Way ANOVA, and tukey tests. **Results**: The results showed that administration of EEJCL can significantly lower LDL levels and blood pressure ($p<0.050$)* at doses of 1.8 g/KgBW, 2.7 g/KgBW and 4.05 g/KgBW *and increase HDL levels at dose* 4.05 g/KgBW is the most optimal dose. ***Conclusion**: EEJCL has potential for development in the treatment of hypertension and dyslipidaemia.*

***Keywords**: Cardiovascular, LDL, HDL, Blood pressure, Jatropha curcas*

INTRODUCTION

Cardiovascular diseases (CVDs), consisting of ischemic heart disease, stroke, heart failure, peripheral artery disease, and several other heart and blood vessel conditions, are the leading cause of global mortality and a major contributor to reduced quality of life. In 2017, CVDs caused around 17.8 million deaths worldwide, equivalent to 330 million years of life lost and 35.6 million more years lived with disability (Mensah et al., 2019).

Coronary atherosclerotic heart disease (CAHD) is characterized by dyslipidemia, manifesting as elevated levels of low-density lipoprotein (LDL) and triglycerides (TG), alongside decreased levels of high-density lipoprotein (HDL). Elevated LDL levels can lead to plaque formation and inflammatory processes, resulting in the progression of atherosclerosis within arterial walls and thrombosis in CAHD. Meanwhile, HDL plays a protective role by reinforcing tissues surrounding arterial walls, inhibiting cholesterol deposition within arteries, and facilitating the repair of damaged endothelial membranes. Conversely, reduced levels of HDL impede the removal of cholesterol (Sun et al., 2022). Evaluation of the lipid profile (triglycerides, LDL cholesterol, HDL cholesterol and total cholesterol) in the blood is one way to identify the causes of hypertension, which is another cause of cardiovascular disease (Fuchs & Whelton, 2020). Research by Flint et al (2019) on the influence of systolic and diastolic blood pressure on cardiovascular explained that both systolic and diastolic blood pressure above the two threshold limits of ≥140/90 mm Hg and ≥130/80 mm Hg significantly contribute to cardiovascular disease risk (Flint et al., 2019).

The prescriber usually used for hypertension and dyslipidaemia are synthetic drugs such as captopril and simvastatin, but the use of herbal medicines is now developing and more preferred for long-term treatment due to their minimal side effects. One potential plant is ***Jatropha curcas*** which is known to contain saponins, polyphenols, and flavonoids that play a major role in treating various diseases, including bacterial and fungal infections as well as acting as antioxidants (Ait Babahmad et al., 2018). According to Sadik et al (2021), reported that administration of ethanol extract of ***Jatropha curcas*** leaf can reduce blood pressure of hypertensive wistar rats and can increase NO levels. In research conducted by Anita et al (2023), reported that administration of ethanol extract of ***Jatropha curcas*** leaf can significantly reduce serum triglyceride levels at doses of 1.8 g/KgBW, 2.7 g/KgBW, 4.05 g/KgBW. Research results on physic nut leaf on HDL and LDL have also been reported by Anigbogu (2015), revealing that ethanol extract of ***Jatropha curcas*** leaf can increase HDL cholesterol concentration thereby reducing LDL cholesterol concentration. This indicates that ethanol extract of ***Jatropha curcas*** can be used for the treatment of cardiovascular disease.

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Please revise this section as suggested by reviewer. You should explain the relation between hipertension, dislipidemia, CVDs and CAHD. Otherwise please use other approach to explain.

Due to the presence of many Jatropha leaf in Indonesia, many studies have examined the activity of Jatropha on blood pressure, LDL levels, and HDL levels. So, the author wants to research the effect of giving jatropha leaf on blood pressure activity, LDL levels, and HDL levels in hypertensive rats given a high-fat diet.

MATERIALS AND METHODS

This study is an experimental study with a pre-post test control group design and has obtained ethical approval from Ahmad Dahlan University with the number 011804052. The test animals were grouped into 7 groups, namely the normal group, negative control, Captopril, Simvastatin, and EEJCL 1.8; 2.7; and 4.05 g/kgBW. The test animals in groups other than normal were induced with 3.75 g/kgBW NaCl for 14 days to produce high blood pressure and a high-fat diet to produce hyperlipidaemia, while the normal group was only given standard feed.

Materials

The materials used in this study were *Jatropha curcas* L. leaves obtained from the Gunung Kidul area of Yogyakarta and has been determined at the Biology Laboratory, Faculty of Applied Science and Technology, Universitas Ahmad Dahlan Yogyakarta with the number 033/Lab.Bio/B/IV/2018, 96% ethanol, Captopril, Simvastatin, NaCl, Na CMC, quercetin standard, gallic acid, Folin Ciocalteau reagent, $AlCl_3$, Na_2CO_3, Silica gel 60 F_{254}, methanol, ethyl acetate, chloroform. All chemicals used were Merck analytical grade. The test animals used were 35 male Wistar strain rats aged 2-3 months with weights of 200-250 grams.

Tools

The tools used included a drying cabinet, blender, glassware, an analytical balance, stirrer, macerator, vacuum, rotary evaporator, water bath, centrifuge, Eppendorf tubes, micropipettes, glassware, vortex, and UV-Vis spectrophotometer.

Methods

Preparation of Extract Ethanol of *Jatropha curcas* Leaf (EEJCL)

As much as 1700 grams of dried *Jatropha curcas* L. leaf powder was macerated using 96% ethanol as a solvent in a ratio of 1: 4, stirred for 3 hours and left to stand for 24 hours. Extraction was carried out 3 times. The extracts were evaporated using a rotary evaporator at 70°C and water bath until a thick extract was obtained (Anita & Bachri, 2023).

Compound Identification using TLC

Thin layer chromatography was carried out with silica gel F_{254} solid phase and mobile phase of hexane: ethyl acetate: formic acid (6:4:0.2) for flavonoid analysis and mobile phase HCl_3: MeOH: H_2O (7:3.5: 1). Sample spots were sprayed with $FeCl_3$ reagent for polyphenols and ammonia vapor for flavonoids and then compared to standard compound spots, and the Rf value of each sample was determined (Saepudin et al., 2023).

Total Flavonoid test

As much as 10 mg ethanol extract of *Jatropha curcas* leaf was dissolved in 10 ml of ethanol p.a and 1 ml was pipetted out of 5 ml. The resulting solution was pipetted 2 ml and added with 2 ml of 2% $AlCl_3$. Absorbance was read with a spectrophotometer at a wavelength of 510 nm. Quercetin standard was prepared by dissolving quercetin in ethanol p.a and made at concentrations of 4, 6, 8, 10, 12 µg/ml. The samples were examined with three replications. The flavonoid content was expressed as equivalent to quercetin (Endah, 2016).

Total Phenolic Test

As much as 10 mg of ethanol extract of *Jatropha curcas* leaves was dissolved in 10 ml of p.a ethanol as solvent and then pipetted 1 ml to 5 ml. The obtained solution was pipetted 300 µl and added 1.5 ml Folin-Ciocalteu reagent. After being left for 3 minutes, 1.2 ml of 7.5% Na_2CO_3 solution was added and left again at room temperature. Absorbance was read with a spectrophotometer at a wavelength of 750 nm. Gallic acid standard solutions were made in concentrations of 15, 20, 25, 30, 35 µg/ml each put into tubes, then added 1.5 ml Folin-Ciocalteu reagent (1:10), then a calibration curve was made of the relationship between gallic acid concentration (µg/ml) and absorbance (Endah, 2016).

Antihypertensive Activity Test

The induced test animals, which was given orally on day 15 until day 21 in the control animal group were given CMC-Na treatment, the Captopril group was given a Captopril suspension at a dose of 4.5 mg/KgBW, and the extract group was given EEJCL 1.8; 2.7; and 4.05 g/KgBW. Blood pressure measurements were carried out on day 14 for pre-treatment data. Then the test sample administration was carried out from day 15 to day 21, during this time span blood pressure measurements were carried out on day 17, 20, and day 22. The rats systolic, diastolic, and mean arterial were measured using the non-invasive blood pressure method using the CODA device. This method uses a tail cuff placed on the rats tail to monitor blood pressure. This CODA device has a VPR (Volume Pressure Recording) sensor, which uses a differential pressure transducer specifically designed to measure blood volume in the rats tail non-invasively.

LDL Test

The induced test animals in the normal and negative groups were given treatment with NaCMC, the positive group was given Simvastatin 0.9 mg/kgBW, and dose groups 1, 2, and 3 were given ethanol extracts of *Jatropha curcas* leaves (EEJCL) namely 1.8; 2.7; and 4.05 mg/kgBW respectively. Blood sampling was carried out twice, before and after treatment, by fasting the rats for ± 12 hours. Blood sampling of 3 mL was carried out through the retro-orbital sinus after

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Any reference the method used?

The results of the total phenolic of ethanol extract of Jatropha leaves content test were 11.03% ± 0.60. The results of measuring total phenolic levels were carried out by making a gallic acid standard curve, which produced a linear regression equation seen in Figure 4, and the results of calculating flavonoid levels in the ethanol extract of Jatropha leaves can be seen in Table 4.

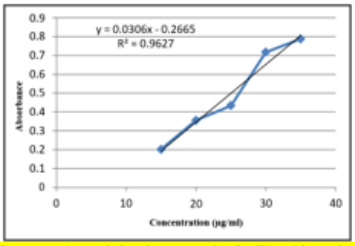

Figure 4. The Concentration and absorbance graph of gallic acid standard solution

Table 4. Total phenolic content of ethanol extract of Jatropha leaves

Extract Weight (mg)	Absorbance	Total Phenolic Content (%)
10,1	0,422	11,1
10,3	0,466	11,6
10,5	0,404	10,4
	Mean ± SD	11,03 ± 0,60

The obtained values were above the total phenol and flavonoid previously studied by Sadik et al (2017) with total flavonoids of 1.48% ± 0.01 and total phenolics of 5.51% ± 0.01. The results obtained differed, possibly due to differences in environmental conditions such as temperature, soil, and plant cultivation processes.

Antihypertensive testing

The study was conducted on 7 groups of test animals each consisting of 5 rats. Blood pressure measurement averages were conducted on day 14, day 17, day 20, and day 22. The results obtained from each measurement can be seen in Tables 5, 6 and 7.

Table 5. Systolic blood pressure measurement results on day 14, day 17, day 20, and day 22

Groups	Dose (g/KgBW)	Average of Systolic blood pressure (mmHg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	119,0±6,51	123,0±9,13	117,0±5,56	120,0±8,24
Control	-	151,0±7,74	145,8±2,77	155,8± 6,91	137,4±5,40
Captopril	0,0045	148,6 ±12,4	122,8±3,19*	118,0±5,65*	121,4±9,55*
EEJCL	1,8	143,2±3,96	126,2±10,98	126,4±12,19*	114,8±9.75*
	2,7	143,8±11,88	141,0±13,43	129,8±18,55*	113,4±8,26*
	4,05	139,6±6,18	130,2±17,15*	127,0±16,53*	118,0±8,71*

*p<0,05 significantly different from the control group

The data of systolic blood pressure measurement (Table 5), it was found that the administration of ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower systolic blood pressure in the blood, where the most effective EEJCL dose in this test was 2.7 g/kgBW, namely a decrease greater than the comparative group (captopril). Previous studies Sadik et al (2021) also found that plants containing flavonoid compounds can lower blood pressure. Flavonoids can inhibit ACE by forming chelate complexes at the active center of ACE, depending on their main structural features. The flavonoid content in the extract, as well as its antioxidant activity, supports its ability as an antihypertensive agent (Guerrero et al., 2012). The results of one-way ANOVA statistical tests on systolic blood pressure obtained a significant value ($p<0.05$), meaning there was an effect of decreasing systolic blood pressure after being given test preparations, so it can be concluded that there is effectiveness of administering ethanol extract of *Jatropha curcas* leaves (EEJCL) as an antihypertensive on male Wistar strain rats.

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How about extraction process/method? will this effecting the results?

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Revise the numbering writting in all tables, (1–9), such as 119,0 should be written as 119.0

The statistical test results of the EEJCL 1.8; EEJCL 2.7; and EEJCL 4.05 groups showed a significant difference ($p < 0.05$) compared to the control group. The Simvastatin groups were significantly different with a value ($p < 0.05$) compared to the control group. The EEJCL 1.8 and EEJCL 4.05 groups showed no significant difference with a value ($p > 0.05$) compared to the Simvastatin group. The EEJCL 2.7 group showed a significant difference ($p < 0.05$) compared to the Simvastatin group. This shows that the administration of EEJCL can lower LDL levels but has not reached normal levels. The data results of the difference in rat LDL levels can be seen in Table 8.

The decrease in blood pressure and LDL is related to the presence of flavonoid compounds. Various studies have proven that flavonoid content can lower blood pressure and LDL by inhibiting angiotensin converting enzyme and binding free radicals and metal ion transitions in inhibiting lipid peroxidation (Loh et al., 2020). Flavonoids have the ability to stop oxidative damage and LDL oxidation. In addition, luteolin derivatives can trigger cholesterol barrier secretion, meaning cholesterol levels decrease. When cholesterol is transported from the intestine to the liver, flavonoids function as inhibitors of the HMGCoA reductase enzyme, the enzyme responsible for converting acetyl-CoA to mevalonate in cholesterol synthesis, thus reducing synthesis (Nuralifah et al., 2020). Thus, the administration of ethanol extract of ***Jatropha curcas*** leaves (EEJCL) for 7 days can lower LDL levels in hypertensive rats given a high-fat diet.

HDL Testing

The study of LDL level measurements was conducted on 7 animal test groups, each consisting of 5 rats. The results of HDL measurements on day 15 and day 22 in each group can be seen in Table 9.

Table 9. HDL level measurement results (mg/dL) after being given Simvastatin and Ethanol Extract of Jatropha curcas Leaves (EEJCL)

Groups	Dose (g/KgBw)	Day15[1)] (Mean ± SD)	Day-22[2)] (Mean ± SD)	Difference (Mean ± SD)	Decrease percentage (%)
Normal	-	34,57 ± 1,17	36,67 ± 0,78	2,09 ± 1,63[a]	5
Control	-	23,39 ± 1,89	26,40 ± 2,38	3,01 ± 2,23[a]	11
Simvastatin	0,0009	24,61 ± 1,21	33,82 ± 0,57	9,18 ± 1,12[b]	27
EEJCL	1,8	24,58 ± 2,35	27,45 ± 1,49	2,87 ± 1,56[a]	10
	2,7	24,58 ± 3,29	29,64 ± 1,49	5,05 ± 2,95[a]	17
	4,05	23,46 ± 2,86	35,60 ± 0,67	12,14 ± 2,32[a,b]	34

[a)] $p<0,05$, significantly different from the simvastatin
[b)] $p<0,05$, significantly different from the control group
[1)] Day 15 after being given high fat feed and given NaCl 3.75 g/KgBW for 14 days
[2)] Day 22 after being given ethanol extract of ***Jatropha curacas*** leaves (EEJCL) for 7 days

The control group; Simvastatin; EEJCL 1.8; EEJCL 2.7; and EEJCL 4.05 groups before treatment had lower HDL levels compared to the normal group (Table 9). This is because groups other than normal were given a high-fat diet containing a lot of cholesterol. HDL is said to be low if the level is <30 mg/dL (Hernáez et al., 2019). Then the HDL levels in each group showed an increase after EEJCL administration. Table 4 shows that there was an increase in HDL levels after being given EEJCL treatment in each group. This shows that ***Jatropha curcas*** leaf ethanol extract is able to increase HDL levels. Consistent with previous research conducted by Anigbogu et al (2015) that ***Jatropha curcas*** leaf ethanol extract can increase HDL levels. The increase in HDL levels occurred after administration of ethanol extract of ***Jatropha curcas*** leaves which was known to contain flavonoid compounds.

In this study, the highest HDL level increase occurred in the EEJCL 4.05 group. With increasing drug doses, the effects given should provide comparable effects with increased doses. Ultimately, with increasing doses, the effects will decrease. This is because the dose can no longer maximally provide effects. This case often occurs in traditional or herbal medicines where the content is no longer a single chemical compound but several types of chemical compounds that work together to provide effects. It is not impossible that with increasing doses, the amount of contained compounds also increases and unwanted reactions occur that can reduce effects (Siskayanti et al., 2017).

The same study was also conducted by Abdulmumin (2020), reporting that extracts of ***Jatropha Curcas*** leaves, peel, stems and roots have hypolipidemic activity and may be useful in managing cardiovascular disease. While the acute toxicity (LD50) of ***Jatropha curcas*** leaf, peel, stem and root extracts was greater than 5000 mg/kg, thus declared practically non-toxic to experimental animals (Mika'il et al., 2020). Administering treatments such as EEJCL containing flavonoids is likely to increase endothelial nitric oxide (eNOS) synthesis, thus increasing NO bioavailability. Flavonoids can act as vasodilators with suitable signaling pathways and structural characteristics for strong vasorelaxant properties (Loh et al., 2020). Therefore, ethanol extract of ***Jatropha curcas*** leaf has potential for development in the treatment of hypertension and dyslipidaemia, so this study will be a reference for further similar topic research in the future and has the potential to lead to the development of more promising antihypertensive alternatives.

CONCLUSION

1. The Ethanol Extract of ***Jatropha curcas*** L. has a total flavonoid content of 4.41% ± 0.04 and a total phenolic content of 11.03% ± 0.60.

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Conclusion should be written as a complete paragraph not listing. Also the conclusion section should not repeating the number/results that has been written in the results and discussion. Please also take a note on the limitation and future direction of the study.

Lampiran 5. Informasi pengiriman hasil revisi ke-2 ke reviewers

Artikel dikirimkan kembali setelah melakukan revisi ke-2 pada tanggal **9 Maret 2024** serta mengirimkan bukti hasil proofreading and editing service dari Dr. Ardian Wahyu Setiawan, M.Ed pada tanggal **19 Maret 2024**.

COMMENT AND RESPONSE

REVIEWER

Comments	**Responses**	**Page**
Please revise this section as suggested by reviewer. You should explain the relation between hipertension, dislipidemia, CVDs and CAHD. Otherwise please use other approach to explain.	Thank you for the review you have given us. We have revised that section	In Page 1 lines 47-58
Mention the standard used	Thank you for the review you have given us. We have revised that section	In Page 2 lines 100
This sentence is confusing. Better state the concentration of sample used	Thank you for the review you have given us. We have revised that section	In Page 2 lines 103 and 108
Any reference the method used?	Thank you for the review you have given us. We've added a reference to the method	In Page 3 lines 122
How about extraction process/method? will this effecting the results?	Thank you for the review you have given us. We have added a sentence that on extraction using the same method	In Page 5 lines 219
Revise the numbering writting in all tables, (1--9), such as 119,0 should be written as 119.0	Thank you for the review you have given us. We have corrected all the writing in the table (1-9)	
Conclusion should be written as a complete paragraph not listing. Also the conclusion section should not repeating the number/results that has been written in the results and discussion. Please also take a note on the limitation and future direction of the study.	Thank you for the review you have given us. We have revised that section	In Page 8 lines 329

Editorial Certificate

DATE ISSUED: 19 March 2024

No. 1687/N/2024

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has been proofread-edited by one or more editors at Prosemantic - Proofreading and Editing Service

Manuscript Title

The Effect of the Ethanol Extract of Jatropha curcas L. Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet

Chief Editor,

PROSEMANTIC
Proofreading-Editing

Dr. Ardian Wahyu Setiawan, MEd. (EdD).

Neither the research content nor the authors' intentions were altered in any way during the editing process. Authors have the ability to accept or reject our suggestions and changes. If you have any questions or concerns regarding the edited document, please contact Prosemantic – Proofreading and Editing Service at prosemantic@gmail.com.

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Lampiran 6. Informasi pemberitahuan artikel di accepted

Artikel telah di accepted oleh Jurnal Farmasi dan Ilmu Kefarmasian Indonesia (JFIKI) pada tanggal **30 Maret 2024**

JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA (JFIKI)
Fakultas Farmasi Universitas Airlangga
Kampus C UNAIR Jl. Dr. Ir. H. Soekarno 60115 Telp. 031-5933150 Fax. 031-5935249
Email: Jfiki@ff.unair.ac.id

Surabaya, 30-3-2024

ID: 51710

Dear Mr. Moch Saiful Bachri,

Your manuscript entitled **"The Effect of the Ethanol Extract of *Jatropha curcas* L. Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet"** written by **Moch Saiful Bachri, Wiki Yuli Anita, Putri Dwi Lestari, Desi Eko Wulansari, Dwi Retno Nengtyas, Muhammad Ma'ruf, Sapto Yuliani, Wahyu Widyaningsih, Laela Hayu Nurani, Daru Estiningsih, Vivi Sofia** has been evaluated by the anonymous reviewers, and discussed with the Chief Editors, and we are please to inform you that your manuscript has been **accepted** for publication in the **Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Volume 11 (2024)** (https://e-journal.unair.ac.id/JFIKI/).

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes

Elida Zairina, MPH., Ph.D., Apt.
Editor-in-chief
Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
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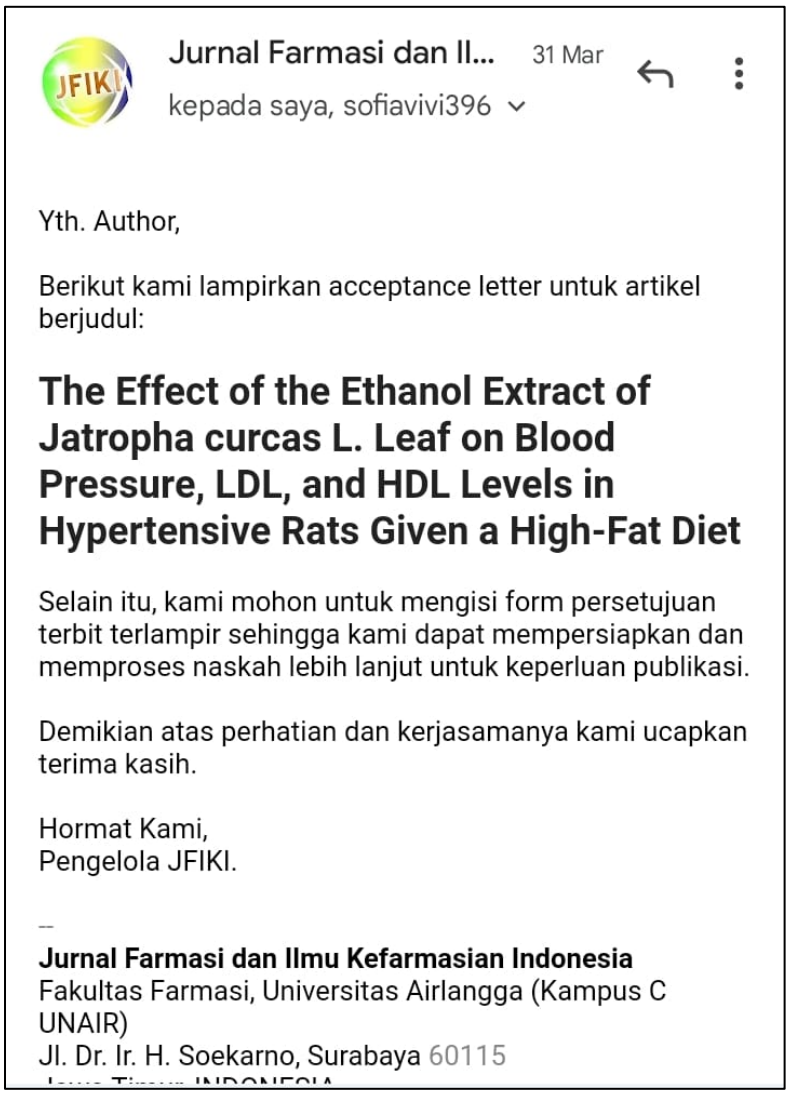
Lampiran 7. Informasi pengisian surat persetujuan publikasi

Pada tanggal **31 Maret 2024**, author mendapatkan email untuk mengisi surat persetujuan publikasi (*latter of approval to publish*).



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kepada saya, sofiavivi396

Yth. Author,

Berikut kami lampirkan acceptance letter untuk artikel berjudul:

The Effect of the Ethanol Extract of Jatropha curcas L. Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet

Selain itu, kami mohon untuk mengisi form persetujuan terbit terlampir sehingga kami dapat mempersiapkan dan memproses naskah lebih lanjut untuk keperluan publikasi.

Demikian atas perhatian dan kerjasamanya kami ucapkan terima kasih.

Hormat Kami,
Pengelola JFIKI.

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Telp. 031- 5933150 Email: Jfiki@ff.unair.ac.id

Letter of Approval to Publish

Through this letter, we agree that the manuscript entitled:

"The Effect of Ethanol Extract of *Jatropha curcas* L. Leaf on Blood Pressure, LDL, and HDL Levels in Hypertensive Rats Given a High-Fat Diet"

Can be published in **Jurnal Farmasi dan Ilmu Kefarmasian Indonesia *online* Volume 11 (2024)** on the following website:

http://e-journal.unair.ac.id/index.php/JFIKI.

Yogyakarta, 1 April 2024

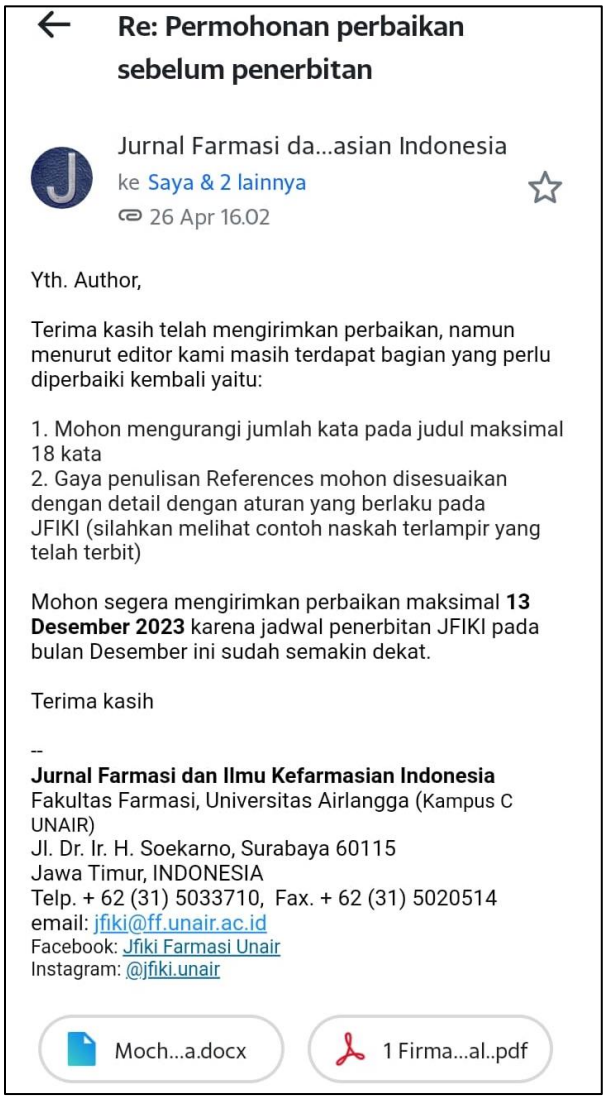
Sincerely,

Author

[Moch. Saiful Bachri]

Lampiran 8. Informasi revisi artikel sebelum penerbitan

Pada tanggal **26 April 2024**, author mendapatkan email untuk melakukan perbaikan artikel sebelum penerbitan.



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Yth. Author,

Terima kasih telah mengirimkan perbaikan, namun menurut editor kami masih terdapat bagian yang perlu diperbaiki kembali yaitu:

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2. Gaya penulisan References mohon disesuaikan dengan detail dengan aturan yang berlaku pada JFIKI (silahkan melihat contoh naskah terlampir yang telah terbit)

Mohon segera mengirimkan perbaikan maksimal **13 Desember 2023** karena jadwal penerbitan JFIKI pada bulan Desember ini sudah semakin dekat.

Terima kasih

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Jl. Dr. Ir. H. Soekarno, Surabaya 60115
Jawa Timur, INDONESIA
Telp. + 62 (31) 5033710, Fax. + 62 (31) 5020514
email: jfiki@ff.unair.ac.id
Facebook: Jfiki Farmasi Unair
Instagram: @jfiki.unair

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26 Apr 16.16

Yth. Author,

Mohon maaf pada email sebelumnya kami salah mencantumkan tanggal deadline. Mohon agar perbaikan **besok 27 April 2024.**

Terima kasih

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Fakultas Farmasi, Universitas Airlangga (Kampus C UNAIR)
Jl. Dr. Ir. H. Soekarno, Surabaya 60115
Jawa Timur, INDONESIA
Telp. + 62 (31) 5033710, Fax. + 62 (31) 5020514
email: jfiki@ff.unair.ac.id
Facebook: Jfiki Farmasi Unair
Instagram: @jfiki.unair

Tampilkan konten yang dipangkas

Lampiran 9. Informasi artikel telah dipublish

Artikel telah publis pada tanggal **30 April 2024**

Current Issue

Vol. 11 No. 1 (2024): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA

Published: 2024-04-30

Home > Archives > Vol. 11 No. 1 (2024): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA > Articles

Jatropha curcas L. Leaf Extract Effects on Blood Pressure and Lipid Levels in Hypertensive Rats with High-Fat Diet

Moch. Saiful Bachri
msaifulbachri@pharm.uad.ac.id
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Wiki Yuli Anita
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Putri Dwi Lestari
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Desi Eko Wulansari
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Dwi Retno Nengtyas
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Muhammad Ma'ruf
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Sapto Yuliani
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Wahyu Widyaningsih
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Laela Hayu Nurani
Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

Daru Estiningsih
Laboratory of Pharmacology, Laboratory of Pharmacology, Faculty of Health Sciences, Alma Ata University, Yogyakarta, Indonesia

Vivi Sofia
Faculty of Pharmacy, Tjut Nyak Dien University, Medan, Indonesia

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Jatropha curcas L. Leaf Extract Effects on Blood Pressure and Lipid Levels in Hypertensive Rats with High-Fat Diet

Moch Saiful Bachri[1*], Wiki Yuli Anita[1], Putri Dwi Lestari[1], Desi Eko Wulansari[1], Dwi Retno Nengtyas[1], Muhammad Ma'ruf[2], Sapto Yuliani[1], Wahyu Widyaningsih[1], Laela Hayu Nurani[1], Daru Estiningsih[3], Vivi Sofia[4]
[1]Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia
[2]Departemen of Pharmacy, School of Health ISFI Banjarmasin, Banjarmasin Indonesia
[3]Laboratory of Pharmacology, Laboratory of Pharmacology, Faculty of Health Sciences, Alma Ata University, Yogyakarta, Indonesia
[4]Faculty of Pharmacy, Tjut Nyak Dien University, Medan, Indonesia

*Corresponding author: msaifulbachri@pharm.uad.ac.id

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Abstract

***Background**: One of the main risk factors for cardiovascular diseases such as coronary atherosclerotic heart disease (CAHD) is dyslipidaemia or high levels of low-density lipoprotein (LDL) and triglycerides (TG) and low levels of high-density lipoprotein (HDL). Hypertension is also a cause of cardiovascular disease. One potential plant to lower LDL levels and blood pressure is Jatropha curcas, which is known to contain saponins, polyphenols, and flavonoids. **Objective**: The purpose of this study was to determine the effect of the ethanol extract of Jatropha curcas leaves (EEJCL) on blood pressure, LDL levels, and HDL levels in hypertensive rats given a high-fat diet. **Methods**: This study is an experimental study with a pretest-posttest control group design on male Wistar strain rats. Rats were divided into seven groups, namely the normal group, control group (induced with NaCl and given a high-fat diet), Captopril group, Simvastatin group, and EEJCL groups given doses of 1.8, 2.7, and 4.05 g/kg BW. The data obtained were analysed using the One-Sample Kolmogorov-Smirnov Test, Homogeneity of Variance, One-Way ANOVA, and Tukey Test. **Results**: The results showed that the administration of EEJCL could significantly lower LDL levels and blood pressure and increase HDL levels ($p < 0.05$) at doses of 1.8, 2.7, and 4.05 g/kg BW, and the dose of 4.05 g/KgBW was the most optimal dose. **Conclusion**: EEJCL has a potential for development in the treatment of hypertension and dyslipidaemia.*

***Keywords**: Cardiovascular, LDL, HDL, Blood pressure, Jatropha curcas*

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INTRODUCTION

several other heart and blood vessel conditions, are the leading cause of global mortality and a major contributor to reduced quality of life. In 2017, CVDs caused around 17.8 million deaths worldwide, equivalent to 330 million years of life lost and 35.6 million more years lived with disability (Mensah *et al*., 2019).

Coronary atherosclerotic heart disease (CAHD) is characterized by dyslipidemia, manifesting as elevated levels of low-density lipoprotein (LDL) and triglycerides (TGs), alongside decreased levels of high-density lipoprotein (HDL). Elevated LDL levels can lead to plaque formation and inflammatory processes, resulting in the progression of atherosclerosis within arterial walls and thrombosis in CAHD. Meanwhile, HDL plays a protective role by reinforcing tissues surrounding arterial walls, inhibiting cholesterol deposition within arteries, and facilitating the repair of damaged endothelial membranes. Conversely, reduced levels of HDL impede the removal of cholesterol (Sun *et al*., 2022).

Evaluation of the lipid profile (triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol) in the blood is one way to identify the causes of hypertension, which is another cause of cardiovascular disease (Fuchs & Whelton, 2020). Research by Flint *et al*. (2019) on the influence of systolic and diastolic blood pressure on cardiovascular conditions explained that both systolic and diastolic blood pressure measuring ≥ 140/90 mm Hg and ≥130/80 mm Hg, respectively, significantly contribute to cardiovascular disease risk.

Hypertension, dyslipidemia, cardiovascular diseases (CVDs), and coronary atherosclerotic heart disease (CAHD) are interconnected conditions that can increase the risk of cardiovascular events. Dyslipidemia is a condition characterized by abnormal levels of lipids in the blood, and it is associated with an increased risk of hypertension. High levels of cholesterol can cause the blood vessels to become narrow and less elastic, leading to increased blood pressure (Hedayatnia *et al*., 2020).

Dyslipidemia is also a significant risk factor for CVDs, including CAHD. When dyslipidemia is present alongside hypertension, the risk of CVDs, including CAHD, increases. This is because both conditions contribute to the process of atherosclerosis, which is the buildup of plaque in the arteries. This plaque can lead to the narrowing and hardening of the blood vessels, reducing blood flow to the heart and increasing the risk of heart attack or stroke (Ariyanti and Besral, 2019). Futhermore, hypertension, dyslipidemia, CVDs, and CAHD are interconnected conditions that can increase the risk of cardiovascular events. Dyslipidemia is associated with an increased risk of hypertension and can exacerbate the risk of CVDs, including CAHD, when present alongside these conditions.

The prescriptions usually used for hypertension and dyslipidaemia are synthetic drugs such as Captopril and Simvastatin, but the use of herbal medicines is now developing and more preferred for long-term treatment due to their minimal side effects. One potential plant is *Jatropha curcas*, which is known to contain saponins, polyphenols, and flavonoids, that not only play a major role in treating various diseases, including bacterial and fungal infections, but also act as antioxidants (Ait Babahmad *et al*., 2018). According to Sadik *et al*. (2021), the administration of the ethanol extract of *Jatropha curcas* leaves can reduce blood pressure of hypertensive Wistar rats and can increase NO levels. In research conducted by Anita *et al*. (2023), it is reported that the administration of the ethanol extract of *Jatropha curcas* leaves can significantly reduce serum triglyceride levels at doses of 1.8, 2.7, and 4.05 g/kg BW. Research results on the effect of the ethanol extract of *Jatropha curcas* leaves on HDL and LDL levels have also been reported by Anigbogu (2015), revealing that the ethanol extract of *Jatropha curcas* leaves can increase HDL cholesterol concentration, thereby reducing LDL cholesterol concentration. This indicates that the ethanol extract of *Jatropha curcas* can be used for the treatment of cardiovascular diseases.

Due to the abundant presence of jatropha plants in Indonesia, numerous studies have examined the activity of the plants on blood pressure, LDL levels, and HDL levels. Therefore, the author intended to research the effect of giving the ethanol extract of *Jatropha curcas* leaves on blood pressure, LDL levels, and HDL levels in hypertensive rats given a high-fat diet.

MATERIALS AND METHODS

This study is an experimental study with a pretest-posttest control group design and has obtained ethical approval from Ahmad Dahlan University with the number 011804052. The test animals were grouped into seven groups, namely the normal group, negative control group, Captopril group, Simvastatin group, and EEJCL groups with doses of 1.8, 2.7, and 4.05 g/kg BW. The test animals in groups other than the normal group were induced with NaCl at 3.75 g/kg BW for 14 days to produce high blood pressure and a high-fat diet to produce hyperlipidaemia, while the normal group was only given standard feed.

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Materials

The materials used in this study were *Jatropha curcas* L. leaves obtained from the Gunung Kidul area of Yogyakarta and determined at the Biology Laboratory, Faculty of Applied Science and Technology, Ahmad Dahlan University, Yogyakarta, with the number 033/Lab.Bio/B/IV/2018, in addition to 96% ethanol, Captopril, Simvastatin, NaCl, Na-CMC, quercetin standard, gallic acid, Folin-Ciocalteau reagent, $AlCl_3$, Na_2CO_3, Silica gel 60 F_{254}, methanol, ethyl acetate, and chloroform. All the chemicals used were Merck chemicals of analytical grade. The test animals used were 35 male Wistar strain rats aged 2–3 months with weights of 200–250 grams.

Tools

The tools used included a drying cabinet, a blender, glassware, an analytical balance, a stirrer, a macerator, a vacuum, a rotary evaporator, water bath, a centrifuge, Eppendorf tubes, micropipettes, a vortex, and a UV-Vis spectrophotometer.

Methods

Preparation of the ethanol extract of *Jatropha curcas* Leaves (EEJCL)

As much as 1,700 grams of dried *Jatropha curcas* L. leaf powder was macerated using 96% ethanol as a solvent in a ratio of 1:4, stirred for 3 hours, and left to stand for 24 hours. Extraction was carried out 3 times. The extract was evaporated using a rotary evaporator at 70 °C and water bath until a thick extract was obtained (Anita & Bachri, 2023).

Compound identification using TLC

Thin layer chromatography (TLC) was carried out with silica gel F_{254} as the stationary phase, the mobile phase of hexane, ethyl acetate, and formic acid in the ratio of 6:4:0.2 for flavonoid analysis, and the mobile phase of HCl_3, MeOH, and H_2O in the ratio of 7:3.5:1. Sample spots were sprayed with $FeCl_3$ reagent for polyphenols and ammonia vapor for flavonoids and then compared to standard compound spots (quercetin serving as a flavonoid standard and gallic acid serving as a phenolic standard). The Rf value of each sample was determined (Susanto *et al*., 2023).

Total flavonoid test

The resulting sample with a concentration of 1% was pipetted at 2 mL and added with 2 mL of 2% $AlCl_3$. Absorbance was read with a spectrophotometer at a wavelength of 510 nm. The quercetin standard was prepared by dissolving quercetin in ethanol p.a at concentrations of 4, 6, 8, 10, and 12 µg/mL. The samples were examined with three replications. The flavonoid content was expressed as quercetin equivalent (Endah, 2016).

Total phenolic test

The resulting sample with a concentration of 1% was pipetted at 300 µL and added with 1.5 mL of Folin-Ciocalteu reagent. After being left for 3 minutes, 1.2 mL of 7.5% Na_2CO_3 solution was added and left again at room temperature. Absorbance was read with a spectrophotometer at a wavelength of 750 nm. Gallic acid standard solutions were made at concentrations of 15, 20, 25, 30, and 35 µg/mL, each being put into tubes and then added with 1.5 mL of Folin-Ciocalteu reagent (1:10). Afterwards, a calibration curve of the relationship between gallic acid concentration (µg/mL) and absorbance was made (Endah, 2016).

Antihypertensive activity test

The induced test animals in the control group were given a Na-CMC treatment, the Captopril group animals were given a Captopril suspension at a dose of 4.5 mg/kg BW, and the animals in the extract groups were given EEJCL at doses of 1.8, 2.7, and 4.05 g/kg BW, respectively. Treatments were applied orally from day 15 to day 21. Blood pressure measurements were carried out on day 14 for pre-treatment data. Blood pressure measurements were carried out on days 17, 20, and 22. The rats' systolic, diastolic, and mean arterial blood pressures were measured by the non-invasive blood pressure method using the CODA device. A tail cuff was placed on each rat's tail to monitor the rat's blood pressure. This CODA device has a VPR (Volume Pressure Recording) sensor, which uses a differential pressure transducer specifically designed to measure blood volume in the rat's tail non-invasively (Stanisavljevic *et al*., 2022).

LDL test

The induced test animals in the normal and negative groups were given an Na-CMC treatment, the positive group animals were given Simvastatin at 0.9 mg/kg BW, and the animals in the extract groups were given EEJCL at doses of 1.8, 2.7, and 4.05 mg/kg BW, respectively. Blood sampling was carried out twice, before and after treatment, with the rats fasting for ± 12 hours. Blood sampling of 3 mL was carried out through the retro-orbital sinus after the rats were anesthetized with ether (Nurmeilis, 2015). The blood was then centrifuged to obtain the serum. LDL cholesterol level data of the hypertensive Wistar rats given a high-fat diet were then analyzed. The enzymatic colorimetric test method was employed to directly measure LDL cholesterol levels.

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Table 1. TLC results on flavonoid content

Sample	Rf	Detection			Flavonoid
		UV 254	UV 366	Ammonia vapor	
Ethanol extract of *Jatropha curcas* leaves	1) 0.50	Yellow	Yellow	Yellow brownish	+
	2) 0.62	Yellow	Yellow	Yellow brownish	+
	3) 0.68	Yellow	Yellow	Yellow brownish	+
	4) 0.87	Yellow	Yellow	Yellow brownish	+
Quercetin	0.53	Greenish yellow	Greenish yellow	Yellow	+

HDL test

The induced test animals in the control group were given a CMC-Na treatment, the Simvastatin group animals were given a Simvastatin suspension at a dose of 0.9 mg/kg BW, and animals in the extract groups were given EEJCL at doses of 1.8, 2.7, and 4.05 g/kg BW, respectively. Blood sampling was carried out twice, before and after treatment, on day 15 and day 22. The obtained blood was separated between the serum and plasma. The serum was prepared with CHOD-PAP reagent and read on a UV-Vis spectrophotometer at a wavelength of 546 nm. Calculations were made on the obtained data to obtain HDL levels in blood.

Data analysis

Data analysis was conducted using SPSS with preliminary tests including the Kolmogorov-Smirnov test to determine if the data were normally distributed or not and the Levene test to determine if the variance was homogeneous or not. If the obtained data were normally distributed ($p > 0.05$) and homogeneous ($p > 0.05$), then it was followed by the parametric one-way ANOVA at a 95% confidence level. The analysis proceeded with a post-hoc test using Tukey test to show significant differences between treatment groups.

RESULTS AND DISCUSSION

Extraction of *Jatropha curcas* leaves

Extraction of dried powder from *Jatropha curcas* leaves resulted in 84.7 g of thick extract from a total of 1.7 kg of dried powder, with a yield of 4.98%.

Compounds contained in *Jatropha curcas* leaves based on TLC testing

The results of thin layer chromatography (TLC) testing of the extract after being passed under ammonia vapor in visible light indicated the presence of flavonoid compounds, with Rf 0.50. The ethanol extract of jatropha leaves was positive for flavonoids, as can be seen from the chromatogram profile in Figure 1. The TLC identification data of the ethanol extract of jatropha leaves can be seen in Table 1.

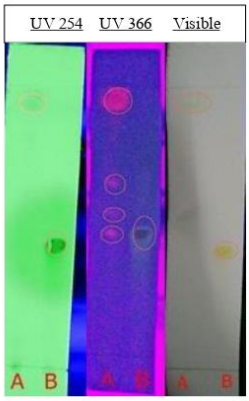

Figure 1. Flavonoid chromatogram profile of the ethanol extract of jatropha leaves: (A) *Jatropha curcas* L. sample; (B) quercetin standard

The results indicated that the ethanol extract of *Jatropha curcas* leaves contained phenolic compounds, with Rf 0.18. The ethanol extract of jatropha leaves was positive for phenolics, as can be seen from the chromatogram profile in Figure 2. The TLC identification data of the ethanol extract of jatropha leaves can be seen in Table 2.

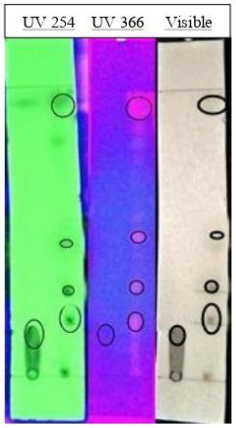

Figure 2. Phenolic chromatogram profile of the ethanol extract of jatropha leaves: (A) *Jatropha curcas* L. sample; (B) gallic acid standard

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Table 2. TLC results on phenolic content

Sample	Rf	Detection			Phenolic
		UV 254	UV 366	$FeCl_3$	
Ethanol	1) 0.18	blackout	Yellow	Black Grey	+
extract of	2) 0.25	blackout	Yellow	Black Grey	+
Jatropha	3) 0.43	blackout	Yellow	Black Grey	+
curcas leaves	4) 0.93	blackout	Yellow	Black Grey	+
Quercetin	0.12	blackout	Blue	Black Grey	+

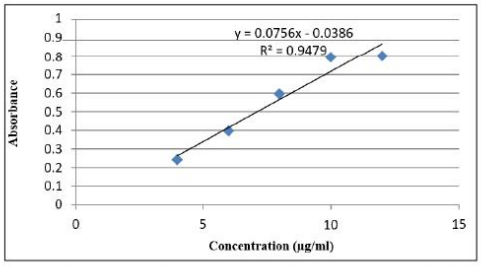

Figure 3. The concentration and absorbance graph of quercetin standard solution

Table 3. Total flavonoid content of the ethanol extract of jatropha leaves

Extract Weight (mg)	Absorbance	Total Flavonoid Content (%)
10.1	0.640	4.43
10.1	0.641	4.44
10.2	0.636	4.36
	Mean ± SD	4.41 ± 0.04

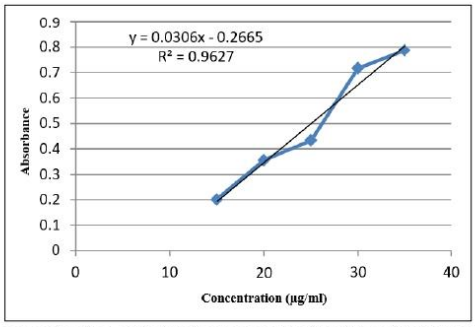

Figure 4. The concentration and absorbance graph of gallic acid standard solution

Table 4. Total phenolic content of the ethanol extract of jatropha leaves

Extract Weight (mg)	Absorbance	Total Phenolic Content (%)
10.1	0.422	11.1
10.3	0.466	11.6
10.5	0.404	10.4
	Mean ± SD	11.03 ± 0.60

Testing of total flavonoid and phenolic contents

Based on testing, the ethanol extract of jatropha leaves had a total flavonoid content of 4.41 ± 0.04%. A quercetin standard curve was developed based on this result, from which a linear regression equation as seen in Figure 3 was produced. The calculation results of flavonoid levels in the ethanol extract of jatropha leaves can be seen in Table 3.

Further testing showed that the ethanol extract of jatropha leaves had a total phenolic content of 11.03 ± 0.60%. A gallic acid standard curve was developed based on this result, from which a linear regression

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equation as seen in Figure 4 was produced. Calculation results on phenolic levels in the ethanol extract of jatropha leaves can be seen in Table 4.

The values obtained were above the total phenolic and flavonoid contents previously calculated by Sadik *et al*. (2017), who conducted extraction using the same method and solvent, where the total flavonoid and phenolic contents obtained were 1.48 ± 0.01% and 5.51 ± 0.01%, respectively. The differences in results were possibly due to differences in environmental conditions, such as temperature, soil, and plant cultivation processes.

Antihypertensive testing

The study was conducted on 7 groups of test animals, each consisting of 5 rats. Blood pressure measurements were conducted on days 14, 17, 20, and 22. The results obtained from each measurement can be seen in Tables 5, 6, and 7.

The data of systolic blood pressure measurement (Table 5) indicate that the administration of the ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower systolic blood pressure. The most effective EEJCL dose according to these data was 2.7 g/kg BW, which could render a decrease greater than the comparative group (Captopril). A previous study by Sadik *et al.* (2021) also discovered that plants containing flavonoid compounds can lower blood pressure. Flavonoids can inhibit ACE by forming chelate complexes at the active centre of ACE, depending on their main structural features. The flavonoid content in the extract, as well as its antioxidant activity, supports the extract's ability as an antihypertensive agent (Guerrero *et al*., 2012). The one-way ANOVA results on systolic blood pressure showed a significant value ($p < 0.05$), meaning that there was an effect of decreasing systolic blood pressure after the application of the preparation. Therefore, it can be concluded that the ethanol extract of *Jatropha curcas* leaves (EEJCL) is effective as an antihypertensive on male Wistar strain rats.

The diastolic blood pressure measurement data (Table 6) indicate that the administration of the ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower diastolic blood pressure. The most effective EEJCL dose according to the data was 2.7 g/kg BW, which could render a decrease greater than the comparative group (Captopril). The one-way ANOVA results on diastolic blood pressure showed a significant value ($p < 0.05$), meaning that there was an effect of decreasing diastolic blood pressure after the application of the preparations. This result supports the conclusion previously drawn.

Table 5. Systolic blood pressure measurement results on days 14, 17, 20, and 22

Group	Dose (g/kg BW)	Mean systolic blood pressure (mm Hg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	119.0 ± 6.51	123.0 ± 9.13	117.0 ± 5.56	120.0 ± 8.24*
Control	-	151.0 ± 7.74	145.8 ± 2.77	155.8 ± 6.91	137.4 ± 5.40
Captopril	0.0045	148.6 ± 12.4	122.8 ± 3.19*	118.0 ± 5.65*	121.4 ± 9.55*
EEJCL	1.8	143.2 ± 3.96	126.2 ± 10.98	126.4 ± 12.19*	114.8 ± 9.75*
	2.7	143.8 ± 11.88	141.0 ± 13.43	129.8 ± 18.55*	113.4 ± 8.26*
	4.05	139.6 ± 6.18	130.2 ± 17.15*	127.0 ± 16.53*	118.0 ± 8.71*

*) $p < 0.05$, indicating a significant difference from the control group

Table 6. Diastolic blood pressure measurement results on days 14, 17, 20, and 22

Group	Dose (g/kg BW)	Mean diastolic blood pressure (mm Hg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	84.8 ± 5.89*	76.6 ± 12.01*	76.8 ± 11.73*	73.0 ± 5.52*
Control	-	115.4 ± 7.19	116.2 ± 20.48	114.8 ± 16.33	92.8 ± 6.30
Captopril	0.0045	100.4 ± 26.85	99.0 ± 14.91	90.6 ± 12.30*	91.8 ± 20.50*
EEJCL	1.8	111.8 ± 6.05	99.6 ± 12.15	91.8 ± 15.62*	78.0 ± 7.71*
	2.7	109.0 ± 10.29	102.0 ± 12.58	95.0 ± 16.07*	77.6 ± 12.46*
	4.05	112.2 ± 9.36	94.4 ± 18.82*	90.0 ± 17.91*	81.8 ± 13.14*

*) $p < 0.05$, indicating a significant difference from the control group

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Table 7. Mean arterial blood pressure measurement results on days 14, 17, 20, and 22

Group	Dose (g/kg BW)	Mean arterial blood pressure (mm Hg) ± SD			
		D-14	D-17	D-20	D-22
Normal	-	98 ± 8.97	92.6 ± 7.40	94.4 ± 5.17	88.4 ± 6.02*
Control	-	127.8 ± 6.26	108.4 ± 12.3	128.2 ± 16.55	110.8 ± 14.75
Captopril	0.0045	123.4 ± 10.23	129 ± 19.27*	98.8 ± 8.40*	93.8 ± 6.64*
EEJCL	1.8	119 ± 5.47	115.6 ± 18.35	103.6 ± 15.37*	89.8 ± 7.56*
	2.7	118.6 ± 10.33	113.2 ± 10.35	106.4 ± 16.63*	90 ± 11.37*
	4.05	117.8 ± 10.32	98 ± 19.91*	105.2 ± 13.4*	90.6 ± 9.76*

*) $p < 0.05$, indicating a significant difference from the control group

Table 8. LDL level measurement results (mg/dL) after application of Simvastatin and the ethanol extract of *Jatropha curcas* leaves (EEJCL)

Group	Dose (g/kg BW)	Day-15[1)] (Mean ± SD)	Day-22[2)] (Mean ± SD)	Difference (Mean ± SD)	Decrease percentage (%)
Normal	-	24.25 ± 2.41	22.92 ± 4.64	1.33 ± 3.79*	5
Control	-	36.64 ± 1.58	48.56 ± 3.01	-11.91 ± 4.01	-32
Simvastatin	0.0009	42.74 ± 1.64	24.70 ± 1.89	18.04 ± 2.91*	42
EEJCL	1.8	37.82 ± 4.97	27.57 ± 3.90	10.24 ± 5.25*	27
	2.7	38.53 ± 2.87	26.16 ± 1.94	12.37 ± 4.02*	32
	4.05	38.47 ± 1.97	24.15 ± 1.22	14.31 ± 1.48*	37

*) $p < 0.05$, indicating a significant difference from the control group
1) Day 15, after being given high-fat feed and NaCl at 3.75 g/kg BW for 14 days
2) Day 22, after being given the ethanol extract of *Jatropha curcas* leaves (EEJCL) for 7 days

The mean arterial blood pressure measurement data (Table 7) show that the administration of the ethanol extract of *Jatropha curcas* leaves (EEJCL) was able to lower the mean arterial blood pressure, where the most effective EEJCL dose in this test was 1.8 g/kg BW, with a decrease greater than the comparative group (Captopril). Blood pressure measurements on days 20 and 22 had already shown significant decreases in blood pressure approaching normal. The statistical test results showed a significant difference between the dose groups and the induced groups, while the statistical results of the dose groups compared to the normal and Captopril groups showed no significant difference. The flavonoid compounds in the *Jatropha curcas* leaf ethanol extract exhibited ACE inhibitory activity, which was induced by the formation of chelate complexes at the ACE active centre; this activity depends on the main structural features of flavonoids. The flavonoid content in the extract, and its proven antioxidant activity, supports the extract's ability as an antihypertensive (Dhianawaty *et al*., 2018). As a result, the blood pressure of test rats in the EEJCL 1.8, EEJCL 2.7, and EEJCL 4.05 groups could be lowered approaching normal.

LDL testing

LDL level measurements were also conducted on all the test groups on days 15 and 22, the results of which can be seen in Table 8.

The statistical test results of the EEJCL 1.8, EEJCL 2.7, and EEJCL 4.05 groups showed a significant difference ($p < 0.05$) from the control group. The Simvastatin group was also significantly different ($p < 0.05$) from the control group. The EEJCL 1.8 and EEJCL 4.05 groups showed no significant difference ($p > 0.05$) from the Simvastatin group. Finally, the EEJCL 2.7 group showed a significant difference ($p < 0.05$) from the Simvastatin group. This shows that the administration of EEJCL could lower LDL levels, but not to the extent of normal levels. The data of the difference in rat LDL levels can be seen in Table 8.

The decreases in blood pressure and LDL levels are related to the presence of flavonoid compounds. Various studies have proven that flavonoids can lower blood pressure and LDL levels by inhibiting angiotensin-converting enzyme and binding free radicals and metal ion transitions in inhibiting lipid peroxidation (Loh *et al*., 2020). Flavonoids have the ability to stop oxidative damage and LDL oxidation. In addition, luteolin derivatives can trigger cholesterol barrier secretion, meaning cholesterol levels decrease. When cholesterol is transported from the intestine to the liver, flavonoids function as inhibitors of the HMGCoA reductase enzyme, the enzyme responsible for converting acetyl-CoA to mevalonate in cholesterol synthesis, thus reducing synthesis (Nuralifah *et al*., 2020). Thus, the administration of the ethanol extract of *Jatropha curcas* leaves (EEJCL) for 7 days can lower LDL levels in hypertensive rats given a high-fat diet.

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Table 9. HDL level measurement results (mg/dL) after application of Simvastatin and the ethanol extract of *Jatropha curcas* Leaves (EEJCL)

Groups	Dose (g/kg Bw)	Day15[1)] (Mean ± SD)	Day-22[2)] (Mean ± SD)	Difference (Mean ± SD)	Decrease percentage (%)
Normal	-	34.57 ± 1.17	36.67 ± 0.78	2.09 ± 1.63*	5
Control	-	23.39 ± 1.89	26.40 ± 2.38	3.01 ± 2.23	11
Simvastatin	0.0009	24.61 ± 1.21	33.82 ± 0.57	9.18 ± 1.12*	27
EEJCL	1.8	24.58 ± 2.35	27.45 ± 1.49	2.87 ± 1.56*	10
	2.7	24.58 ± 3.29	29.64 ± 1.49	5.05 ± 2.95*	17
	4.05	23.46 ± 2.86	35.60 ± 0.67	12.14 ± 2.32*	34

*) $p < 0.05$, indicating a significant difference from the control group
1) Day 15, after being given high-fat feed and NaCl at 3.75 g/kg BW for 14 days
2) Day 22, after being given the ethanol extract of *Jatropha curacas* leaves (EEJCL) for 7 days

HDL testing

At last, HDL level measurements were conducted on the test groups. The results of these HDL level measurements on day 15 and day 22 in each group can be seen in Table 9.

Before treatment, the control, Simvastatin, EEJCL 1.8, EEJCL 2.7, and EEJCL 4.05 groups had lower HDL levels compared to the normal group (Table 9). This was because groups other than the normal group were given a high-fat diet containing a lot of cholesterol. HDL is said to be low if the level is < 30 mg/dL (Hernáez *et al*., 2019). Then, the HDL levels in each group showed an increase after EEJCL administration. Table 4 shows that there was an increase in HDL levels after the application of the EEJCL treatment in each group. This shows that *Jatropha curcas* leaf ethanol extract is able to increase HDL levels. Previous research by Anigbogu *et al*. (2015) also discovered that *Jatropha curcas* leaf ethanol extract can increase HDL levels. The increase in HDL levels occurred following the administration of the ethanol extract of *Jatropha curcas* leaves, which is known to contain flavonoid compounds.

In this study, the highest HDL level increase occurred in the EEJCL 4.05 group. The effects resulted should go hand in hand with increasing doses. However, higher doses will have decreased effects. This is because the dose can no longer maximally provide effects. This case often occurs in traditional or herbal medicines, in which case these medicine no longer contain a single chemical compound, but several types of chemical compounds that work together to provide effects. It is not impossible that with increasing doses the amount of contained compounds also increases and unwanted reactions that can reduce effects occur (Siskayanti *et al*., 2017).

A similar study was conducted by Abdulmumin (2020), who reported that extracts of *Jatropha Curcas* leaves, peel, stems, and roots have hypolipidemic activity and may be useful in managing cardiovascular diseases. The acute toxicity (LD50) of *Jatropha curcas* leaf, peel, stem, and root extracts was found to be greater than 5,000 mg/kg, thus declared practically non-toxic to experimental animals (Mika'il *et al*., 2020). Administering treatments such as flavonoid-containing EEJCL is likely to increase endothelial nitric oxide (eNOS) synthesis, thus increasing NO bioavailability. Flavonoids can act as vasodilators with suitable signaling pathways and structural characteristics for strong vasorelaxant properties (Loh *et al*., 2020). In other words, the ethanol extract of *Jatropha curcas* leaves has a potential for development in the treatment of hypertension and dyslipidaemia. This study can be a reference for further research on similar topics, with the potential to lead to the development of more promising antihypertensive alternatives.

CONCLUSION

The ethanol extract of *Jatropha curcas* L. (EEJCL) leaves contains flavonoid and phenolic compounds. The administration of EEJCL can reduce blood pressure significantly in terms of systolic, diastolic, and average arterial blood pressure. In addition, it can increase HDL levels and reduce LDL levels in the blood of hypertensive rats given a high-fat diet. Therefore, it is concluded that the ethanol extract of *Jatropha curcas* L. (EEJCL) leaves has a potential for development in the treatment of hypertension and dyslipidaemia.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.S.B., W.Y.A., P.D.L., D.E.W., D.R.N.; Methodology, M.S.B.; Validation, S.Y., W.W., L.H.N.; Formal Analysis, M.M., L.H.N.;

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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