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Efficacy of Putri Malu Leaf Plant (*Mimosa Pudica Linn*) as Hepatoprotectors on Ibuprofen Induced Hepatic Damage in White Mice (*Mus Musculus*)

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Abstract

Background: Putri Malu leaf plants (*Mimosa pudica Linn*) contain flavonoid compounds beneficial as hepatoprotectors. Putri Malu leaf plant extract can be useful to prevent problems such as Ibuprofen-induced hepatic damage, but studies that focus on this topic remain scarce in Indonesia.

Objective: To prove the extracted content of the leaves of the Putri Malu plant (*Mimosa pudica Linn*) as a hepatoprotector of hepatic damage in mice (*Mus musculus*) induced by Ibuprofen

Method: This randomized post-test control group design was conducted at the Experimental Animal Laboratory, Faculty of Veterinary Medicine, Universitas Airlangga. A total of 28 mice were treated with four conditions then underwent SGOT and SGPT blood laboratory tests.

Results: Group P1 (placebo) had SGOT and SGPT levels averaging 23.87 mg/dl and 13.45 mg/dl, group P2 (ibuprofen dose 7 mg/kg BW) had SGOT and SGPT levels of 29.13 mg/dl and 19.10 mg/dl, group 3 (Putri Malu extract 35 mg/kg BW) had SGOT and SGPT of 24.05 mg/dl and 13.56 mg/dl, and group 4 (ibuprofen dose 7 mg/kg BW and Putri Malu extract of 35 mg/kg BW) showed SGOT and SGPT levels of 28.23 mg/dl and 18.35 mg/dl. The four groups had different mean SGOT and SGPT levels ($P < 0,000$).

Conclusion: Leaf extract of the Putri Malu leaf plants (*Mimosa pudica Linn*) has a chemical effect on hepatoprotection, as shown by the decrease in SGOT and SGPT levels.

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INTRODUCTION

The Putri Malu leaf plants (*Mimosa pudica Linn*) in Indonesia treat various diseases such as infections, diseases caused by free radicals, and even food preservatives¹. This plant contains compounds that are useful as anti-inflammatory, expedite urination, anti-virus, anti-fungal, antibacterial, anti-hypertensive, and hepatoprotective².

Ibuprofen is a type of nonsteroidal anti-inflammatory drugs (NSAID) that has antipyretic and analgesic properties. Ibuprofen is a propionic acid derivative that is analgesic with not very strong anti-inflammatory properties³. According to Kempa and Krzyzanowski, in 2016, patients often overuse and increased the dose by their own, which might induce hepatic cell damage⁴. This condition can be prevented by several bioactive compounds that have hepatoprotective effects, i.e., flavonoid.

Flavonoids act as antioxidants and hepatoprotective, antibacterial, and others⁵. This compound can be found in herbs, including Putri Malu leaf plants. It can be used as a hepatoprotector but study regarding this effect on Ibuprofen-induced hepatic damage remains scarce, especially in Indonesia where herbs have been used since ancestor's generation. This study aims to know the effect of Putri Malu leaf extract as hepatoprotection against Ibuprofen-induced hepatic damage.

METHODS

This type of experimental research is a post-test control group design⁶. This was using the animal population of white mice (*Mus musculus*) from the Surabaya Pusvetma laboratory. Determination of the sample size using the Federer formula obtained a sample of 28 mice. The independent variable is the extract of the leaves of the Putri Malu leaf plant (*Mimosa pudica Linn*), and the dependent variable is the reduction in the levels of Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) in white mice induced Ibuprofen and given the extract of the leaves of the Putri Malu leaf plant.

The study was conducted in 4 different treatment groups. The first group was given a placebo for 30 days (P1), the group that was given Ibuprofen at a dose of 7 mg/kg BW/day for 30 days (P2), the group that was given the Putri Malu leaf plants extract dosage of 35 mg/kg BW/day for 30 days (P3), and the group that was given Ibuprofen at a dose of 7 mg/kg BW/day and extract of the leaves of the Putri Malu plant at a dose of 35 mg/kg BW/day for 30 days.

Data processing of SGOT and SGPT levels of the blood collected will be coded, edited, entered, and cleaned. Then grouped according to research variables and presented in tables, frequency distribution, crosstables, and graphs. A different test was performed using the one-way ANOVA method.

RESULT

Serum Glutamic Oxaloacetic Transaminase (SGOT) levels in each treatment group can be analyzed in table 5.1 as follows:

Table 5.1 Serum Glutamic Oxaloacetic Transaminase (SGOT) levels

Group	N	Mean SGOT (mg/dl)	SD	p
P1	6	23,87	1,075	0,000
P2	6	29,13	0,927	
P3	6	24,05	2,889	
P4	6	28,23	0,965	

P1: Placebo, P2: Ibuprofen, P3: Putri Malu Leaf Extract, P4: Ibuprofen and Putri Malu Leaf Extract

Our analysis of SGOT level after treatment showed in Table 5.1 that group P2 had the highest SGOT level among other groups while group P3 had the lowest SGOT level (29.13 ± 0.927 mg/dl and 24.05 ± 2.889 mg/dl respectively).

We used the Shapiro Wilk normality test to determine the distribution of the results. The results were that all groups ($p > 0.05$) could be defined as normally distributed. In addition, we also used the Levene test to know the homogeneity of the results. The test showed a significant value of 0.199 ($p > 0.05$), which means the four groups have the same variance.

To know the differences between groups, we analyzed the results by using the one-way ANOVA test. The results revealed that there was a significant difference in SGOT levels in the four groups ($P = 0,000$)

The subsequent analysis was carried out by the posthoc LSD test with the following results:

Table 5.5 Posthoc LSD Test of SGOT

Group Treatment	Control	Difference Mean SGOT (mg/dl)	P
P1	P2	-5,267	0,000*
	P3	-0,183	0,852
	P4	-4,367	0,000*
P2	P1	5,267	0,000*
	P3	5,083	0,000*
	P4	0,900	0,365
P3	P1	0,183	0,852
	P2	-5,083	0,000*
	P4	-4,183	0,000*
P4	P1	4,367	0,000*
	P2	-0,900	0,365
	P3	4,183	0,000*

P1: Placebo, P2: Ibuprofen, P3: Putri Malu Leaf Extract, P4: Ibuprofen and Putri Malu Leaf Extract

The Posthoc LSD Test conducted on the SGOT results in table 5.5 showed significant differences in the P1 vs. P2, P1 vs. P4, P2 vs. P3, and P3 vs. P4 groups.

Serum Glutamic Pyruvate Transaminase (SGPT) levels in each treatment group can be analyzed in table 5.6 as follows:

Table 5.6 Serum Glutamic Pyruvate Transaminase (SGPT) levels

Group	N	Mean	SD	p
P1	6	13,45	1,050	0,000
P2	6	19,10	0,998	
P3	6	13,567	2,572	
P4	6	18,35	1,692	

P1: Placebo, P2: Ibuprofen, P3: Putri Malu Leaf Extract, P4: Ibuprofen and Putri Malu Leaf Extract

Our analysis of SGPT level after treatment showed in Table 5.6 that group P2 had the highest SGPT level among other groups while group P1 had the lowest SGPT level (19.10 ± 0.998 mg/dl and 13.45 ± 1.050 mg/dl respectively).

We used the Shapiro Wilk normality test to determine the distribution of the results. The results were that all groups could be defined as normally distributed. In addition, we also used the Levene test to know the homogeneity of the results. The test showed a significant value of 0.291 ($p > 0.05$), which means that the four groups have the same variance.

To know the differences between groups, we analyzed the results by using the one-way ANOVA test. The results revealed that there was a significant difference in SGPT levels in the four groups ($P = 0,000$)

The subsequent analysis was carried out by the posthoc LSD test with the following results:

Table 5.10 Posthoc LSD Test of SGPT

Group Treatment	Control	Difference Mean SGPT (mg/dl)	P
P1	P2	-5,650	0,000*
	P3	-0,117	0,907
	P4	-4,900	0,000*
P2	P1	5,650	0,000*
	P3	5,533	0,000*
	P4	0,750	0,454
P3	P1	0,117	0,907
	P2	-5,533	0,000*
	P4	-4,783	0,000*
P4	P1	4,900	0,000*
	P2	-0,750	0,454
	P3	4,783	0,000*

P1: Placebo, P2: Ibuprofen, P3: Putri Malu Leaf Extract, P4: Ibuprofen and Putri Malu Leaf Extract

The Posthoc LSD Test conducted on the SGPT results in table 5.10 showed significant differences in the P1 vs. P2, P1 vs. P4, P2 vs. P3, and P3 vs. P4 groups.

DISCUSSION

The study was conducted to determine the effect of the extract of Putri Malu leaf plant (*Mimosa pudica Linn*) on reducing SGOT and SGPT levels in mice's hepatic (*Mus musculus*) induced by Ibuprofen. Mice were chosen because of their small size compared to rats, short breeding time, and have 99% gene similarities with humans. Toxicology shows that male rats are more sensitive than female rats, so they are used for testing⁷. The treatment group was divided into four, then the SGOT and SGPT levels were measured from the mice's blood on the 31st day.

Group P1 was given a placebo aquadest treatment. A placebo administration is essential in a study because it affects the sample's psychological condition and triggers the body's chemical effects in relieving pain and triggering pain. However, it does not affect the actual disease or medical condition⁸. Aquadest is used because it does not significantly affect medical conditions, especially for SGOT and SGPT levels. Also, several previous studies have been carried out, including research by Khristivanie using aquadest as a placebo in his research⁹. The SGOT and SGPT levels in the P1 group were still in the normal range. The range of normal AST levels in white mice (*Mus musculus*) is 23.2-48.4 mg/dl, and the range of normal ALT levels in white mice (*Mus musculus*) is 2.1-23.8 mg/dl¹⁰. SGOT and SGPT are enzymes marking the presence of hepatic damage detected through peripheral blood circulation. SGOT and SGPT are not only used as markers of hepatic damage but can be used as laboratory tests to assess damage to other organs, one of which is the heart¹¹. However, SGOT and SGPT are often associated and used as an enzyme to detect hepatic tissue damage.

In a study conducted on group P2, the sample was given the drug ibuprofen at a dose of 7 mg/kg BW per day. This dose was given as a sample treatment based on the reference of previous research on the effect of olive oil on the hepatotoxicity of ibuprofen-induced female rats conducted by Abbas M T. et al.¹¹. Ibuprofen's dosage was 40 mg/kg BW for 30 days, and the results were observed on the 31st day. This dose was proven to cause hepatotoxic pathophysiological activity in female rats used as the study sample. Hepatotoxicity in the previous study was detected through histopathological examination of the hepatic tissue, AST and ALT levels, and several other investigations. The dose was then converted using a dose conversion formula so that a value of 7 mg/kg BW per day was obtained for the animal species of mice (*Mus musculus*). Ibuprofen is a non-steroidal anti-inflammatory analgesic drug or NSAID for short. NSAIDs are more toxic than classic antipyretics¹². SGOT and SGPT levels in the group given the ibuprofen drug showed the highest levels than the other groups. This is due to a pathophysiological process caused by giving Ibuprofen. The drug ibuprofen will first be absorbed through the gastrointestinal tract, especially by the intestines and colon, then enter the blood plasma and are bound by plasma proteins and then carried to the hepatic to undergo a detoxification process. However, this detoxification process only excretes 90% of Ibuprofen's intact levels so that it accumulates in the hepatic and aggravates the body's

xenobiotic metabolic process, resulting in hepatic cell damage¹². The ALT/AST enzyme is found in the heart, hepatic, skeletal muscle, kidney, brain, pancreas, spleen, and lung cells. 30% of AST is located in the hepatic cells' cytoplasm, while the remaining 70% is located in the hepatic cells' mitochondria, while the ALT/SGPT enzyme can be found in the hepatic, heart, muscle, and kidney cells¹³.

In the third treatment group, the Putri Malu leaf extract's dosage refers to the research results conducted by Johnson K et al. In this study, the leaves extract of the Putri Malu leaf plants given in a 200 mg/kg BW dose in Wister albino rats showed a hepatoprotective effect on hepatic damage induced by CCl₄ compounds¹⁴. Besides it also refers to Arianti's research using extract doses of embarrassing female leaves of 153 mg/kg BW, 612 mg/kg BW, and 1200 mg/kg BW, all of which show hepatoprotector activity from the observation of SGOT and SGPT levels¹⁵. A 200 mg/kg BW dose was finally used as a treatment from these two studies. Furthermore, the dose was converted using the formula from rats to mice so that the dose was 7 mg/kg BW. This group had lower SGOT and SGPT levels than P2 and P4 groups given ibuprofen induction. However, this level was slightly higher than that of the P1 group. The P3 group had levels that were not too high compared to the P2 and P4 groups because the administration of the Shy Princess plant's leaves did not cause any hepatic damage. The leaf extract of the Putri Malu leaf plant (*Mimosa pudica* Linn) contains flavonoid compounds. Several flavonoid compounds have been shown to have benefits in the hepatoprotective field⁵. Although the extract of the leaves of the embarrassed daughter plant has a hepatoprotector effect, the flavonoid compounds from this extract are reported to have a stimulating effect on the enzymatic activity of RNA and protein produced through DNA biosynthesis and cell proliferation for hepatic regeneration, which only occurs when the hepatic is damaged⁵. The absence of hepatoprotective operation triggered the absence of a pathophysiological mechanism of hepatic or hepatotoxic damage in this population. This pathologic is indicating SGOT and SGPT enzymes' levels close to the value of the control group.

Ibuprofen and Putri Malu leaf extract were given the same dose as the other group in the fourth group. Both treatments in this group were given using oral swabs, with Ibuprofen given first, then after 8 hours after giving the leaves extract of the Putri Malu leaf plant. The time lag between Ibuprofen and the shy daughter's administration aims to avoid drug reactions with extracts that can cause biased data. As an analgesic dose works in 30-90 minutes, Ibuprofen will decrease performance in 120 minutes¹⁶. Meanwhile, according to Carter, W.C. and B.R. Brown, Ibuprofen which is absorbed through the digestive tract or orally, has a very short half-life ranging from 1.8 to 2 hours, and its levels will drop drastically in plasma after 2 hours so that in the administration of the two compounds there is no chemical reaction¹⁷. SGOT and SGPT levels in the P4 group were classified as having a significantly higher difference when compared to the P1 and P3 groups. Ibuprofen accumulates in the hepatic and aggravates the body's xenobiotic metabolic process, resulting in hepatotoxic damage. The presence of hepatic cell damage was indicated by increased SGOT and SGPT enzymes than the control group's levels. However, the levels of the P4 group were lower than the SGOT levels in the P2 group. This is because the P4 group was given the

leaves of the embarrassed daughter plant. Putri Malu leaf plants, especially in the leaves, are extracted so that quercetin-type flavonoids are obtained. Quercetin has two effects on the body; the first is to stimulate the enzymatic activity of RNA and protein through DNA biosynthesis to increase the regeneration and proliferation of hepatic cells⁵. This ability can overcome cell and tissue damage caused by ibuprofen drug induction. While the second effect, flavonoid compounds, has cyanidin 3-O-B glucoside (C3G) anthocyanins, which can increase cAMP, resulting in increased GCLC secretion causes a decrease in ROS and proapoptosis signals and activation of protein kinase A (PKA). Decreased ROS, proapoptotic signaling, and PKA activation also affect the repair of hepatotoxic cells and hepatic tissue⁵.

Groups P1 and P3, which theoretically were in the range of normal SGOT and SGPT levels, followed the study results. However, on the other hand, the SGOT and SGPT levels in the P2 and P4 groups have an average that is still within the standard threshold. Several things allow the effects of Ibuprofen to be less than optimal, giving it a hepatotoxic effect. The dosage has a very significant effect on the drug's performance and the effect given to the body. Zulizar's research states that paracetamol given at recommended doses has a safe effect, but in large doses, it causes digestive disorders and hepatic function to death¹⁸. Several other things can also cause the quality of the dosage and the overall drug content to be damaged so that the drug's performance in the body is ineffective. These include the storage of drugs such as temperature, humidity, cleanliness, ventilation and air quality, light, and the presence of separators or segregation. Temperature is the most dominant factor because it causes material damage from drugs¹⁹. The quality of Ibuprofen used in the study was terrible and affected the results of AST and ALT levels in mice's hepatic, which should have made AST and ALT levels exceed the normal range. The storage of Ibuprofen in this study was not completely protected from exposure to direct sunlight. Because drug storage exposed to direct sunlight can damage the drug content²⁰.

In the P3 group study results, SGOT and SGPT levels increased compared to the control group even though this difference was very slight. This may be caused by several things related to the Putri Malu leaf plant extract. The extract was not previously subjected to phytochemical testing in this sample, so it was unknown which compounds were contained in the daughter's extract and how many flavonoids were contained in the daughter's extract, which was expected to be the main compound used as the key in this study. These include alkaloids, glycosides, flavonoids, and tannins²¹. The unknown level of flavonoid compounds in the extract and other compounds in the extract cause biased research results.

Based on previous research used as a reference dose for embarrassed girls, it has been stated that the dose used in this study which is the result of the previous conversion, has been able to prove its magnitude as a hepatoprotector. This can also get other data refracting factors in the form of storage time. The storage time treatment affects the quality and content of the extract itself²². Another study on the effect of temperature and storage time of Dayak onion extract on antibacterial activity conducted by Seja Y et al., stated that the extract's temperature and storage time also had a significant effect on the content of the extract understudy, especially as antibacterial²³. This study

also revealed that the extracted storage used had an optimal impact on room temperature storage compared to the refrigerator. In the extract used in this study, storage was carried out in the refrigerator so that there was a possibility of a decrease in the Putri Malu leaf plant quality. This research's strength is that the research flow method is relatively straightforward and does not require special skills. Besides, Ibuprofen and Putri Malu leaf plants used as research materials are easy to obtain. This study's weakness is that the SGOT and SGPT levels of the sample before treatment are not known, so it is difficult to make a definite final reference for changes in SGOT and SGPT. Also, limitations in extract storage can affect the extract's quality so that the SGOT and SGPT levels in the study are still in the normal range.

CONCLUSION

The leaf extract of the Putri Malu plant (*Mimosa Pudica* Linn) showed a chemical hepatoprotective effect on hepatic damage in mice (*Mus Musculus*) induced by Ibuprofen by looking at the decrease in levels of SGOT and SGPT produced in the hepar of white mice induced by Ibuprofen.

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