

Liver Organ Impairment Due to the Consumption of Kratom Leaves (*Mitragyna speciosa* Korth.)

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ABSTRACT

This study was aimed to evaluate the administration effects of kratom leaves extracts on the liver of mice (*Mus musculus*). The total of 25 mice was divided into five groups, respectively; (A) without treatment, (B) treatment with distilled water at 0.50 ml/20 g body weight, (C) treatment of kratom leaves extracts with a dosage of 0.15 mg/20 g body weight, (D) treatment of kratom leaves extracts with a dosage to 0.30 mg/20 g body weight and (E) treatment with a dosage of silymarin at 0.70 mg/20 g body weight. All those treatments were completed in seven consecutive days. On day 8, blood withdrawal and liver dissection were executed. The average levels of AST enzyme in the treatment groups respectively showed 22.81 U/L (A), 23.30 U/L (B), 34.86 U/L (C), 40.68 U/L (D), and 25.44 U/L (E), ($p < 0.05$). Whereas, the average levels of ALT exposed respectively at 17.96 U/L (A), 18.35 U/L (B), 29.13 U/L (C), 33.59 U/L (D), and 20.68 U/L (E), ($p < 0.05$). The average scoring for the treatment groups resulted in 0.33, 0.67, 1.33, 1.67, and 0.67, respectively, with $p < 0.05$. Hence, it was concluded that the higher doses of the extracts of kratom leaves administered during the treatment, the more severe damage the liver organ became.

Key words: ALT, AST, Kratom leaves, Liver organ.

INTRODUCTION

Kratom (*Mitragyna speciosa* Korth) is one of the plant types widely growing in African and Southeast Asia^{1,2}, as well as in the territory of the Pacific Islands.¹ In Southeast Asia, kratom is mainly found in the territory lands of Thailand and Malaysia^{3,4}, including Indonesia.⁴ This plant has its unique names in each area, for instance, kratom in the region of Thailand, biak-biak in the region of Malaysia⁵, while purik in the territory of Indonesia, especially in Kabupaten Kapuas Hulu called by the local people. Kratom is a type of woody plant with a height of up to 15-20 meters.

Traditionally, people in Malaysia, Thailand, and Southeast Asia utilise kratom leaves as a botanical medicine for a drug of diarrhoea, diabetes, and blood circulation.⁶ In addition, Gong *et al.*⁷ also reported that the kratom leaves are beneficial to treat fever, malaria, diarrhoea, muscle pain, inflammation, and hypertension. In Indonesia, traditionally, kratom leaves are used to cure diarrhoea, muscle pain, lower blood pressure, as well as a stamina booster.

The results of previous studies showed that the main compounds contained in kratom leaves are the classes of alkaloids, i.e., mitragynine.^{2,8-13} According to Lesiak *et al.*¹⁴ mitragynine has also been revealed in other plants. Furthermore, if compared to *Mitragyna rotundifolia*, mitragynine is only detectable in the leaves of *Mitragyna speciosa* Korth.¹⁵ Mitragynine is also suggested to have properties such as opioids¹⁶⁻¹⁸; correspondingly Carpenter *et al.*¹⁹ also revealed that mitragynine has the activity of antinociceptive. However, excessive

administration of mitragynine may increase locomotor activities spontaneously; thus, it could potentially promote a drug-induced property of kratom leaves, which even resulted in the severity of side effects of opioids.^{20,21} Besides, Abdullah *et al.*²² also demonstrated that kratom has a stimulant property as a psychoactive herb even in a low dose; on the contrary, it will have such opioids effects when consumed at higher doses. Moreover, the abuse use of kratom also may cause poisoning and drug withdrawal symptoms.²³ In line with that, Osborne *et al.*²⁴ disclosed that a 47-year-old person was diagnosed with *drug-induced liver injury* (DILI) after consuming kratom for 21 consecutive days.

Various results of previous studies demonstrated that the medicines belonging to the class of opioids are codeine²⁵ and paracetamol²⁶. These drugs will undertake metabolism in the body. Specifically, paracetamol undergoes metabolism through the process of glucuronidase, sulfatase, and oxidation by isoenzymes of the cytochrome P-450, which take place in the heart, then will be excreted through the kidneys. The process of oxidation by isoenzymes of the cytochrome P-450 will alter the paracetamol into *N-acetyl-p benzoquinone-imine* (NAPQI).^{27,28} Not only paracetamol, but does codeine also belong to the class of opioid drugs, which undergoes the same process of metabolism in the liver. The presence of the enzyme CYP2D6 mainly plays a role in the codeine alteration into its active form of morphine. Polymorphism in the gene CYP2D6 affects the metabolic activity of the enzymes coded. The polymorphism in CYP2D6 generated four types of metabolism, i.e., *extensive metabolizer* (EM), *intermediate metabolizer* (IM), *poor metabolizer* (PM), and *ultra-rapid metabolizer* (UM).²⁵

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Liver is one of the responsible organs, which has an essential function in the metabolism of drugs.^{29,30} Also, liver plays a role in the metabolism of carbohydrates, protein, and fat.^{29,31} Liver belongs to the organ system of a body which is vital in the setting of a variety of physiological processes and is closely related to the metabolism of nutrients and xenobiotics that are primarily exposed to any hazardous substances entering the body.³²⁻³⁶ Damage on the liver will undoubtedly affect the function of the liver itself. This damage is characterized by the presence of increased enzyme levels of alanine transaminase (ALT) and aspartate transaminase (AST) in blood serum.^{32,33,37} Besides, the liver damage is also identified by the increased levels of alkaline phosphatase (ALP), total bilirubin, and total protein in blood serum.³⁸

Correspondingly, the utilization of kratom leaves for the community and the possibility of the negative impact caused by the consumption of kratom leaves, including information about the liver organ that plays a role in the metabolism of drugs, this study was aimed to determine the effects of the extract of kratom leaves against the liver organ.

MATERIAL AND METHODS

Collection of plant materials

Fresh kratom leaves were collected from the garden community in the area of the Village of Nanga Nyabau, North Putussibau Subdistrict, Kapuas Hulu Regency, West Kalimantan Province. The identification of the authentic plants was performed and declared by the Laboratory of Biology, Faculty of Mathematics and Natural Sciences, Tanjungpura University with a letter numbered 045/A/LB/FMIPA/UNTAN/2018.

Experimental animals

Experimental animals used in this study were male mice of the strain Balb/C, aged 2-3 months with the bodyweight ranging between 24-36 grams. All trial animals were collected from the Laboratory Centre of Food and Nutrition Studies, Gadjah Mada University, Yogyakarta, Indonesia. Experimental animals were placed in the acclimatization for 14 days before treatments. During acclimatization, the experimental animals were fed with standard feed, drank *ad libitum*, and were observed their health through weighing the bodyweights. The whole procedure associated with the maintenance and treatment of the experimental animals has already met the ethical requirements stated by the Commission of Ethics of Animals, University of Respati Yogyakarta on the letter numbered 217.2/UNRIYO/PL/IX/2018.

Extraction

The dried leaves of 285 g were extracted by using the solvent of distilled ethanol 96%. Samples were then immersed at room temperature for 24 hours. The immersion was done three times by adding new ethanol at each repetition. After that, the filtrate was then concentrated by using a *vacuum rotary evaporator*. The obtained extracts were a total of 19.01 g with a submerged yield of 6.67%. The extraction process was implemented, referring to the Harborne method.³⁹

The Administration Effect of The Extracts of Kratom Leaves on The Liver of Mice

A total of 25 mice were divided into five groups, with each group of 5. Group A was the group without treatment (control group). Group B received distilled water of 0.50 ml/20 g body weight. Group C was treated with the extracts of kratom leaves with a dosage of 0.15 mg/20 g body weight. Group D received the extracts of kratom leaves with a dosage of 0.30 mg/20 g body weight. At the same time, group E was executed with the administration of silymarin at 0.70 mg/20 g body weight. Treatments were given for seven consecutive days; on the 8th day, it continued for withdrawing blood samples and removing the liver organ. The measured parameters were the enzyme levels of aspartate

transaminase (AST) and alanine transaminase (ALT) in blood serum, as well as an overview of the histopathological series of the dissection liver organ.

Blood biochemical examination

Blood samples were drawn from the *orbital sinus*. The obtained blood collections were then centrifuged at 4000 rpm for 15 minutes. Then the serum was separated and put into eppendorf tubes. Subsequently, the measurement of the enzyme levels of *alanine transaminase* (ALT) and aspartate transaminase (AST) was performed using a kit of DiaSys (Diagnostic System) by the UV-Test method.

Liver histopathology

The animals were sacrificed through cervical dislocation. The removed livers were then processed routinely, for staining with haematoxylin-eosin (HE).⁴⁰ The overview of the liver histopathology was observed under a light microscope, and changes appeared were scored (Table 1).

Data analysis

This study was conducted using a completely randomized design. Data on blood levels of ALT, AST, and liver scoring were statistically analysed by using SPSS 20, following the test of Duncan at level 5%.

RESULTS AND DISCUSSION

Indonesia has a diversity of plant species, which is traditionally used in folk medicine. Treatment by utilizing medicinal plants is widely performed because it is relatively easy to find, and the cost incurred to acquire it is also relatively cheap. More than that, people believe that the side effects of plant drugs compared to synthetic ones are relatively low. Nevertheless, the usage of plants in disease treatments still requires the accuracy of the doses used and the period consumption. Due to excessive usage, it is not likely to cause serious health problems.

Kratom is an herbal remedy that originates from Southeast Asia that has the main compound in the form of mitragynine.^{2,9,10,11-13} Mitragynine in pharmacological view specifies the presence of medicinal properties such as opioids.^{41,42} Smith *et al.*⁴² reported that communities in Southeast Asian countries, such as Malaysia and Thailand, have been long using kratom leaves by chewing, smoking, or brewing into a tea. Even by the people of villages in the region of Southern Thailand, kratom leaves are used to treat coughs, diarrhoea, muscle pain, and hypertension.^{43,44} Scientifically, it was reported that kratom could function as a stimulant if administered at low doses; on the contrary, it might potentially lead to a sedative effect, analgesic, and euphoria if given at high doses.^{41,45} Research conducted by Halpenny⁴⁶ and Yusoff *et al.*⁴⁷ also exhibited that the administration of mitragynine could trigger someone to become addicted, hence kratom may potentially become a dangerous drug.

The consumption of kratom leaves will accordingly result after drinking its decoction. The decoction water of the kratom leaves will enter and go into the digestive tract, then be absorbed by the intestines. After that, these materials will undergo the process of metabolism in the liver. Due to the frequent exposure to a wide variety of materials that enter the body, this undoubtedly provokes the liver to be the most susceptible organ to damage.^{32,33,38,48} The current study was performed to evaluate the condition of the liver due to consuming kratom leaves, and the results of this finding were presented in Table 2, Table 3, and Figure 1.

Blood contains various substances that can provide a scientifically thorough explanation for the physiological condition of an individual.³⁵ One of the substances containing in the blood is an enzyme, and enzyme levels in the blood may suggest an indicator of the health state on individuals. The enzyme level of AST and ALT is a parameter function of the liver that is the most sensitive factor because changes in levels will quickly indicate a specific state if there is damage to liver cells.^{32,34,36,37,38,48}

Table 1: Scoring degree of liver damage.

Score	Description
0	Not found specific changes
1	Liver cells underwent hydropic and fatty degeneration in low degree evenly
2	The liver cells underwent fatty degeneration and steatosis in medium degree, which was multifocal.
3	The liver cells underwent fatty degeneration, steatosis, and dystrophy in severe degree, which was multifocal.

Table 2: The average enzyme levels of the alanine transaminase (ALT) and aspartate transaminase (AST) in mice administered with the extracts of kratom leaves for seven consecutive days.

Treatment Groups	The Average Enzyme Levels	
	AST (U/L)	ALT (U/L)
Without Treatment	22.81 ± 0.49 ^a	17.96 ± 0.34 ^a
Distilled water of 0.50 ml/20 g body weight	23.30 ± 0.34 ^a	18.35 ± 0.41 ^a
Extracts of kratom leaves at 0.15 mg/20 g body weight	34.86 ± 0.93 ^c	29.13 ± 0.34 ^c
Extracts of kratom leaves at 0.29 mg/20 g body weight	40.68 ± 0.59 ^d	33.59 ± 0.43 ^d
Silymarin at 0.70 mg/ 20 g body weight	25.44 ± 1.01 ^b	20.68 ± 0.95 ^b

Description:

*) The same letters in the same column indicated not significantly different (p>0.05)

**) The numbers listed after the symbol ± indicated the standard deviation (SD)

Table 3: Histopathological scoring of the liver of mice.

Treatment Groups	Scoring
Without treatment	0.33 ± 0.58 ^a
Distilled dose of 0.50 ml/20 g body weight	0.67 ± 0.58 ^{ab}
Extract of kratom leaves at 0.15 mg/20 g body weight	1.33 ± 0.58 ^{ab}
Extract of kratom leaves at 0.30 mg/20 g body weight	1.67 ± 0.58 ^b
Silymarin dose of 0.70 mg/ 20 g body weight	0.67 ± 0.58 ^{ab}

*) The same letters in the same column indicated not significantly different (p>0.05)

**) The numbers listed after the symbol ± indicated the standard deviation (SD)

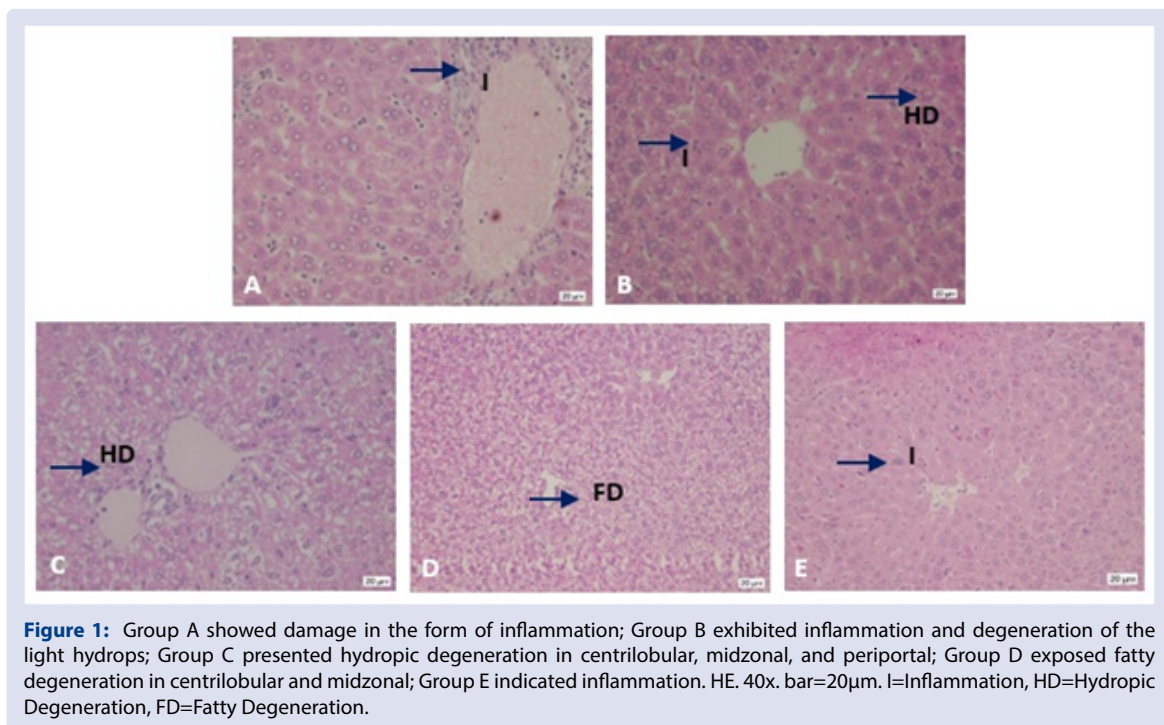


Figure 1: Group A showed damage in the form of inflammation; Group B exhibited inflammation and degeneration of the light hydrops; Group C presented hydropic degeneration in centrilobular, midzonal, and periportal; Group D exposed fatty degeneration in centrilobular and midzonal; Group E indicated inflammation. HE. 40x. bar=20µm. I=Inflammation, HD=Hydropic Degeneration, FD=Fatty Degeneration.

From the results of this study, it was displayed an overview of the levels of AST and ALT enzymes (Table 2), including the images shown from histopathological liver assessment (Figure 1. and Table 3). This result was sufficiently meaningful on the administration of kratom leaves extracts where the increased levels of ALT and AST enzymes occurred, and this increase indicated the presence of damage to the liver cells. In line with the results of this study, Buraimoh *et al.*³² and Domitrović *et al.*³³ expressed that the elevated levels of liver enzymes in the blood suggested that the liver experienced damage in a certain degree which was characterized by histopathological assessment in terms with the presence of lesions, degeneration, necrosis, and steatosis.

Overall, the results of this study revealed that the average levels of the ALT and AST enzymes and the histopathological overview of the liver of mice in the group without treatment and distilled water were relatively close to the group treated with silymarin; despite statistically the average levels of ALT and AST and scoring of the liver showed significantly different ($p < 0.05$). On the other hand, the group of silymarin compared to the group administered by the kratom leaves extract, which showed the presence of improvement, was quite high on average levels of ALT and AST enzymes as well as the changes that appeared on the histopathological images. Likewise, the results of this study demonstrated that the higher the dose of kratom extracts given then the higher the average levels of ALT and AST enzymes, and the broader changes occurred on histopathological images.

Silymarin is a compound of the flavonoid groups found in fruits of the plant *Silybum marianum*.⁴⁹ *Silybum marianum* is a medicinal plant with efficacy as a hepatoprotective.^{48,50} Silymarin is reported to have such antioxidant effects^{51,52}, also anti-inflammatory and immunomodulatory effects.⁵² One of the previous researches on the effects of silymarin in patients with *non-alcoholic fatty liver disease* (NAFLD) also exhibited the ability improvement of the level of enzymes in the liver and insulin resistance.⁵³

The results of several previous studies revealed that the occurrence of fatty degeneration might be caused by a component in the alkaloid-derived doses of a sample test.⁵⁴ Correspondingly, *mitragynine* is an alkaloid metabolite contained in kratom.^{6,44} In addition to mitragynine, Ponglux *et al.*¹² reported that in the leaves of the kratom are also contained 7α -hydroxy-7H-mitragynine, paynantheine, speciogynine, and speciociliatine. Moreover, other compounds are also confined in the kratom leaves such as ajmalicine, corynantheidine, isomitrephylline, mitraphylline, and isocorynantheidine, as well as the flavonoids epicatechin, daucosterol saponins, triterpenoid saponins quinovic acid 3-O- β -D-quinovopyranoside and quinovic acid 3-O- β -D-glucopyranoside, including some derivatives from a group of glycosides such as 1-O-feruloyl- β -D-glucopyranoside, benzyl- β -D-glucopyranoside, 3-oxo- α -ionyl-O- β -D-glucopyranoside, roseoside, vogeloside, and epivogeloside.¹³ Similarly, with regards to the content contained in kratom leaves, Prozialeck *et al.*⁵⁵ stated that the usage of kratom leaves on a long-term basis with large doses might trigger sedative effects, emotional disturbances, weight loss, kidney disorders, and addiction. Nevertheless, Raini⁵⁶ reported that the effects of kratom would depend on the dose amounts administered; in lower doses, it may have a stimulatory effect, yet in higher doses, it may cause a mild narcotic effect, but not the strong one. The higher the doses of kratom leaves administered in a specific period during treatments, the more severe the damage in the liver developed.

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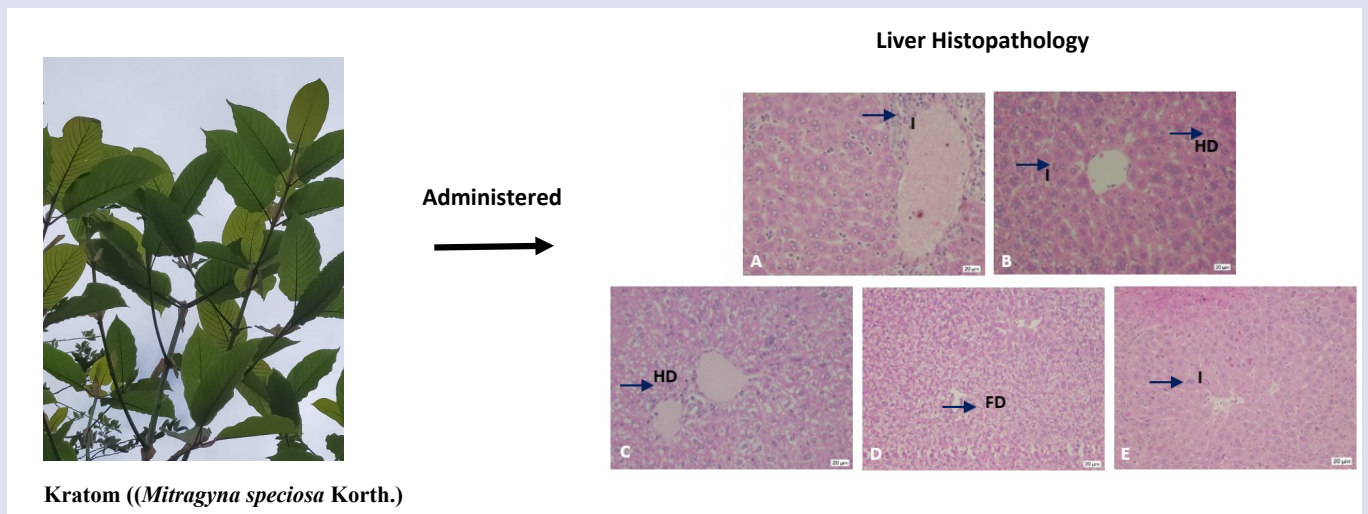
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GRAPHICAL ABSTRACT



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