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Effect of Kratom Extract Administration on Histopathological Picture of Kidney in Wistar Rats

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ABSTRACT

Background: Kratom or ketum or Mitragyna speciosa Korth is a tropical plant of the Rubiaceae family native to Southeast Asia (Muang Thai, Indonesia, Malaysia, Myanmar, Philippines) and Papua New Guinea. Kratom contains more than 40 types of alkaloids, including mitraginin, 7-hydroxymitraginin, painantein, specioginin, speciosiliatin, several types of flavonoids, terpenoids, saponins, and several types of glycosides. Research examining the effect of kratom extract on wistar rats is still limited, so researchers are interested in conducting research on the effect of kratom extract (Mitragyna speciosa) on histopathological images in the kidneys using wistar rats (Rattus novergicus).
Aim: to determine the effect of kratom extract on the histopathological picture of the kidneys of Wistar rats.
Methods: This study is an experimental with post test only control group design that uses wistar rats as the object of research, with 1 control group (5 wistar rats) and 1 treatment group (5 wistar rats) with simple randomization.
Results: The number of wistar rats with a control group of 5 wistar rats and treatment of 5 wistar rats found that all rats in the control group showed a degree of 0 or normal based on histopathology of kidney damage; the treatment group had a significant relationship with $p = 0.005$ ($p < 0.05$), where rats receiving kratom extract tended to show a higher kidney histopathology damage score.
Conclusion: Administration of kratom causes abnormalities in the histopathological picture of the kidneys in the form of hydropic degeneration (narrowing of the tubule lumen) and the appearance of hyaline casts.
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1. Introduction

Kratom, also known as Mitragyna speciosa, is a plant native to Southeast Asia and has long been used as a traditional medicine. Globally, an estimated 5-10 million people use kratom, with the highest prevalence in Southeast Asia. In the United States, kratom is estimated to be used by 1.5-3 million people. In Indonesia, the epidemiological data of kratom is still limited, but several studies show that the prevalence of its use is in the range of 0.5-2%.

Healthy kidney function is essential for maintaining fluid and electrolyte balance in the body. Kratom, when used in certain doses, has been identified as a substance that has the potential to affect kidney function. Some studies on experimental animals, such as mice, have shown that the compounds in Kratom can affect blood pressure and disrupt blood flow to the kidneys. This can negatively impact kidney health and lead to impaired kidney function.[1] High doses of kratom may cause damage to the kidneys, such as glomerular shrinkage and damage to the renal tract.[2]

This study aimed to investigate the effects of kratom extract administration on the renal histopathological findings in Wistar rats. With hypothesis of this study is that kratom administration will induce changes in the renal histopathological features of Wistar rats.

2. Methods

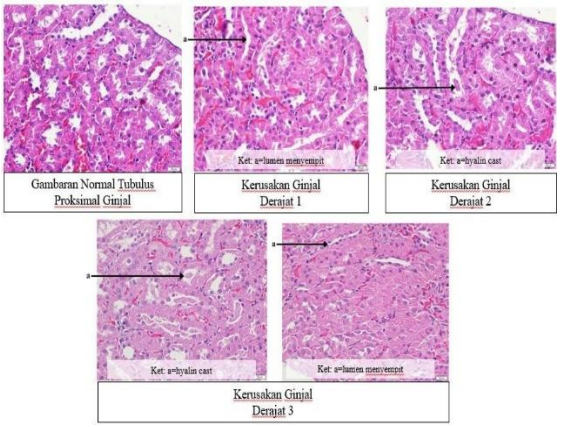
This research is experimental with a post test only control group design that uses wistar rats as the object of research, the number of rats is 10. The rats were grouped by simple random sampling into 2 groups, with five mice each. Before the study was conducted, the mice were acclimatized for 7 days. No mice died during acclimatization. On the 8th day, the rats were given treatment according to their

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respective groups. Mice in the treatment group wgiven kratom extract as much as 20 mg/kgBW for 21 days while mice in the control group will not. The rats were terminated by anesthesia using chloroform and then terminated by cervical dislocation after 21 days of treatment. The collected data will be managed using a computer program with univariate and bivariate data analysis in the form of frequency and percentage tables.

Research ethics were obtained from the Medical and Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Diponegoro University.

3. Result



The results of histopathological examinations showed minimal to moderate damage in the kratom extract group. Abnormalities that appear in the form of narrowing of the lumen of the proximal tubules caused by swelling of the renal tubule tissue, otherwise known as hydropic degeneration, as well as the appearance of *hyaline casts* on the lumen of the proximal tubules.

Kratom Giving Group

Degree of Damage Histopatholo gy of the Kidney	Control	Treatment	p
Degree 0	5 (100%)	0 (0%) 0.005*	
Degree 1	0 (0%)	1 (20%)	0,005*
Degree 2	0 (0%)	3 (60%)	
Degree 3	0 (0%)	1 (20%)	

The table above shows the histopathological results of kidney damage in wistar rats based on differences in treatment. Based on the above data, it was found that all mice in the control group showed degrees 0 or normal based on histopathology of kidney damage. Meanwhile, in the treatment group, the majority of the rat sample (60%) showed a score of 2 or mild; followed by Degree 1 (minimum) and Degree 3 (Medium), 20% each. Rats with grade 4 (severe) or grade 5 (necrosis) kidney damage were not obtained Based on the hypothesis test with the Mann-Whitney test between the administration of kratom extractOn the degree of kidney damage histopathologically, the results were obtained with a significant relationship with p=0.005 (p<0.05), where rats who received the extract

Kratom tends to show a higher histopathological damage score of the kidneys.

4. Discussion

The results of the study showed that there was a significant effect of giving kratom extract 20 mg/kgBW/day during 21 days to the degree of histopathological damage of the kidney of Wistar rats (p=0.005). The group of wistar rats given kratom extract 20mg/kgBW/day for 21 days showed a higher degree of renal histopathological damage (20% degree 1; 60% degree 2; and 20% degree 3) compared to the control group (100% degree 0). In samples with kratom extract, a picture of hydropic degeneration was obtained which was characterized by swelling of tubule tissue that caused a narrowing of the lumen of the tubules. In addition, there is also hyaline cast which can be an indicator of kidney disorders.

These results are in line with a previous study by Ilmie et al with 500 mg/kgBW of extract, showing hydropic degeneration in both the medulla and the renal cortex. In this study, cellular casts were also seen in the lumens of the tubules in the treatment group.3 Another study by Masae et al. showed results that supported that the kratom group showed hydropic degeneration in the form of glomerular swelling, which indicates kidney damage, on histopathological examination compared to the other groups.[1]

A study by Srimangkornkaew et al that compared the effects of giving kratom extract at doses of 250, 500, and 1000 mg/kgBW in wistar rats during 14 days showed the appearance of hyaline casts even minimally in the lumen of the treatment group rats.[4] A study by Sabetghadam et al. (2013) also showed that kidney damage appears to be in the form of swelling of the Bowman's capsule and renal tubule tissue. Interestingly, the study did not show any renal histopathological abnormalities in the group of mice that received doses of 1 and 10 mg/kgBW of kratom extract.[5]

In addition to lowering blood flow to the kidneys, mitraginine can also cause dehydration by increases the frequency of urination through the activation of adrenergic receptors. An increase in the concentration of substances in the urine can form structures, one of which is hyaline cast which is a protein cylinder consisting of Tamm-Horsfall protein formed in the renal tubules. Although not always related to pathological conditions, hyaline cast can be a sign of increased urine concentration due to dehydration which if chronically occurring can worsen kidney conditions.[8]

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Higher doses (5-15 grams) give symptoms like opiate compounds, which have an analgesic and sedative effect.14 How kratom analgetic works by binding to opioid receptors of the central nervous system that control pain. Mitragyne and 7-hydroxy-mitragyne can block the transmission of pain signals to scramblers, thereby reducing the perception of pain in mice. The sedative effects that kratom induces not only control pain but can affect sleep regulation and alertness. When kratom binds to receptors in the brain, it can lower alertness levels and cause sedative effects, in which case it can lead to deeper sleep or relaxation.15 While in this study a dose of 20mg/kgBW was used with a weight of 250-300 grams of wistar rats, the amount of kratom received by a rat every day is 5-6 mg which will provide an analgesic and sedative effect. Therefore, this study shows that gastric irritation is caused by sedation effects that have the potential to cause digestive problems such as gastric ulcers. Meanwhile, heavy sedation can result in dehydration and disorders of the kidneys.

Some studies have shown moderate dependent effects if kratom is used for more than 6 months. Therefore, kratom has a high potential for abuse, but it still has limited medical benefits and can lead to dependence. Kratom itself is a narcotic group II, other examples such as methadone, morphine and fentanyl that have a dependency effect but still have medical benefits. According to some sources, kratom belongs to the narcotics class because it has the same effects as opioids, such as anti-pain and increases euphoria.[12]

In the kidneys, it is more at risk if you have a previous kidney disorder and can experience the accumulation of harmful kratom metabolites. However, this kidney disorder is rare in normal kidney function.

The kidneys are in charge of filtering out kratom metabolites and other byproducts, but they do not come into direct contact with the active compound in high doses. Some studies report kratom side effects are more common in the gastrointestinal tract. More serious kidney problems such as kidney failure or acute kidney damage are less commonly reported and usually occur in individuals who previously had kidney problems.[11]

Overall, although kratom has potential therapeutic benefits in herbal medicine, its use should be considered with caution, especially related to the risk of gastrointestinal disorders. More research is needed to deeply understand the effects of kratom on the kidneys and ensure the safety of its use in the long term.

5. Conclusion

The administration of kratom causes abnormalities in the histopathological picture of the kidneys in the form of hydropic degeneration (narrowing of the lumen of the tubules) and the appearance of hyaline casts or hyaline cylinders.

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