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Biochemical Serum Changes in the Liver and Kidney of Hyperuricemia Rats Exposed to Ethanolic Leaf Extract of Hantap (*Sterculia coccinea* Jack)

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Abstract: High uric acid levels can increase oxidative stress in the kidneys causing glomerular damage and tubular ischemia. In addition, it also causes hepatocyte injury so that uncontrolled hyperuricemia will cause liver damage. This study aims to determine the effect of Hantap leaf extract (*Sterculia coccinea* Jack) on kidney and liver function in rat hyperuricemia. This study was a quasi-experimental study with a post-test only control group design. This study used 30 rats induced with chicken liver juice and potassium oxonate and then given Hantap leaf ethanol extract therapy at doses of 100, 200 and 400 mg/kg BW. Data on urea, creatinine, SGOT and SGPT levels were statistically tested using the ANOVA and Post-hoc Duncan tests. While data on uric acid levels used the T test and Anova. Significantly different results compared to negative controls were found in the group given Hantap leaf extract at doses of 100, 200 and 400 mg/kg BW on uric acid, creatinine, ureum, SGOT and SGPT levels. The results of the study prove that administering Hantap leaf extract can improve kidney and liver function in hyperuricemic rats.

Keywords: Antioxidant; Gout; Hepatoprotective; Hantap; Neuroprotective

Introduction

Gout is a long-term inflammatory arthritis condition characterized by consistently high serum uric acid levels (hyperuricemia), leading to the buildup of monosodium urate (MSU) crystals in joints, tendons, and other tissues (Maiuolo et al., 2016). One common symptom is intense acute pain in the lower extremity joint, known as a gout flare, which typically peaks rapidly, often within a few hours (Ragab et al., 2017). Hyperuricemia, the condition of having elevated levels of urate in the blood, is the product of purine metabolism and a significant risk factor for gout. It plays a crucial role in the development of this disease (Skoczyńska et al., 2020). Hyperuricemia is a primary precursor to gout arthritis and renal disease and is strongly associated with metabolic syndromes like hypertension, diabetes mellitus, non-alcoholic fatty liver disease, and dyslipidemia. Therefore, early management of hyperuricemia is essential (Jaruvongvanich et al., 2017; Skoczyńska et al., 2020; Lee et al., 2021).

Serum uric acid affects an estimated 38 million Americans, and its prevalence is rising globally as developing nations embrace Western diets and lifestyles (Butler et al., 2021). According to Basic Health Research (2018), in Indonesia, the prevalence of hyperuricemia is 32% among individuals under 34 years old, and 68% among those over 34 years old, with rates increasing annually (Kirana & Fatimah, 2022).

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The function of the kidneys is to excrete end products or metabolic waste products of the body, such as urea, creatinine, and uric acid. When hyperuricemia occurs, the filtration function of the kidneys increases. If hyperuricemia continues for a long time, kidney function can decrease, leading to pathological conditions such as kidney failure. This important role will cause problems if the kidneys fail, as metabolites such as urea and creatinine will increase (Mahadita & Suwitra, 2021; Gherghina et al., 2022).

Hyperuricemia can induce liver damage because uric acid is one of the hepatotoxic substances. Uric acid is one of the pro-inflammatory damage-associated molecular patterns (DAMPs) recognized by Toll-Like Receptors (TLR) and triggers an inflammatory reaction. Hepatocyte damage will induce the release of the chemokine monocyte chemoattractant protein-1 (MCP-1). Hepatocyte cell death is common in liver disease due to inflammation (Kushiyama et al., 2016; Sari et al., 2020).

Serum glutamic oxasaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are enzymes whose presence and levels in the blood are used as markers of impaired liver function. These enzymes are normally found in liver cells, but liver damage will cause liver enzymes to be released into the bloodstream, causing their levels to increase (Rasyid et al., 2020).

The primary strategy for treating hyperuricemia involves developing xanthine oxidase inhibitors that are more effective at lowering uric acid levels in the plasma and urine (Cicero, et al., 2021). However, the hypouricemic medications currently in use have various side effects that restrict their use in patients. Consequently, there is an urgent need to explore new hypouricemic agents (Cicero et al., 2021). Hence, it's essential to investigate available anti-hyperuricemic agents, particularly extracts from certain medicinal plants (Le, 2024).

Several plant species are commonly employed in treatment, including Hantap or *Sterculia coccinea* Jack, a well-known medicinal plant used for many diseases (Mahbub et al., 2019; Yuliet et al., 2023). Secondary metabolites in plants, such as flavonoid and alkaloid compounds, are believed to inhibit xanthine oxidase and superoxidase, thus lowering uric acid levels in the blood. These flavonoids, phenolic, and alkaloid compounds in plants can serve as treatments for gout by inhibiting xanthine oxidase activity (Abdulhafiz et al., 2020; James & Paul, 2023). Previous studies have shown that hantap leaf extract contains high levels of alkaloid, phenolic, and flavonoid compounds (Yuliet, et al., 2023). Previous studies have also proven that hantap leaf extract has activity as a xanthin oxidase inhibitor and can reduce uric acid levels from hyperuricemia (≥ 1.4 mg/dL) to normal (<1.4 mg/dL) in mice (Muzuni et al., 2023). Therefore, this study aims to further investigate the role of hantap leaf extract in ameliorating oxidative stress and physiological changes in hyperuricemia model by evaluating certain biochemical parameters (urea, creatinine, SGOT dan SGPT).

Method

This study is an experimental study with a research design using a randomized block design (RAK) method with a posttest only control group design approach, utilizing 30 male Wistar rat test animals divided into 6 groups. The animal model of hyperuricemia used chicken liver juice and potassium oxonate 250 mg/kg BW as an inducer. In vivo, research procedures and laboratory animal care protocols were strictly followed per the guidelines of the animal care committee of the Department of Pharmacy, Tadulako University. The in vivo experimental protocol was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Tadulako University, Number: 4606/UN 28.1.30/KL/2024.

Plant collection

Hantap leaves was collected from plants growing in a natural population in Palu, Central of Sulawesi, Indonesia. The plant was authenticated at Laboratorium Biosistematika Tumbuhan, Biologi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Tadulako, Palu, Sulawesi Tengah (No 762/UN28.1.28/BIO/2023).

Preparation of Plant Extract

The hantap leaves were washed under running water to remove soil and dust particles, then wet sorted, and air-dried in a place not exposed to direct sunlight. The dried plant materials were grounded into a fine powder using an electrical blender. Hantap leaves as much as 1,662 grams were macerated using 12 liters of 96% ethanol solvent. The extraction process was carried out for 1x24 hours while stirring occasionally, then the macerate was separated. The filtration process was repeated with the same type of solvent as much as 2.5 L for 5 days, all the macerate was collected and then evaporated at a temperature of 60 °C until a thick extract was obtained. The extract was stored in a cool and dry place for future experimental use.

Phytochemical screening

The phytochemical analysis of hantap leaf extracts was performed to confirm the presence of specific chemical families. This was determined through solubility tests, characteristic reagent color reactions, and precipitation. The tests were conducted on organic extracts. Alkaloids were identified using Mayer,

Dragendorff, and Wagner reagents; catechin and gallic tannins with ferric chloride; triterpenoid and steroid through the Liebermann reaction; saponins by their ability to form foam; and flavonoids were revealed through a reaction with cyanidin (Hayat et al., 2020).

Animal Model

Young adult male Wistar rats (2-3 months old, weighing 150-200 g) were randomly selected, labeled, and acclimated for one week to laboratory conditions before any experimental manipulation. The rats were housed in the animal facility with unlimited access to standard laboratory feed and sterile tap water until they were used for experiments. Cages and water bottles were cleaned every three days. All efforts were made to minimize pain, stress, and suffering of the experimental animals. The inclusion and exclusion criteria are as follows: Inclusion criteria: healthy condition indicated by good appetite. Exclusion criteria: Sick rats, deceased rats or rats with visible anatomical abnormalities (defects)

Hyperuricemia Model in Rats and Drug Administration

Induction of 50% chicken liver juice as much as 2 mL was carried out every day for eight days and potassium oxonate 250 mg/kg BW was induced on the first and eighth days intraperitoneally (Afiah et al., 2023). On the eighth day, the test animals were induced with chicken liver juice, and 30 minutes later they were given potassium oxonate intraperitoneally. After 1 hour of induction, each treatment was given according to the group. Then 1 hour later the levels of uric acid, creatinine, urea, SGOT, and SGPT were measured.

The experimental mice were divided into 6 groups, with 5 mice in each group:

Group 1: As a normal control, 0.5% Na-CMC suspension was given without induction

Group II: Given 0.5% Na-CMC suspension as a negative control in rat hyperuricemia

Group III: Given allopurinol suspension at a dose of 81 mg/kg BW as a positive control in rat hyperuricemia

Group IV: Given ethanol extract suspension of hantap leaves (EEDH) at a dose of 100 mg/kg BW in rat hyperuricemia

Group V: Given ethanol extract suspension of hantap leaves (EEDH) at a dose of 200 mg/kg BW in rat hyperuricemia

Group VI: Given ethanol extract suspension of hantap leaves (EEDH) at a dose of 400 mg/kg BW rat hyperuricemia

Collection of Blood

Blood sampling for measuring uric acid levels was carried out on day 0 before induction (H0) and day 8 (H8), while for measuring creatinine, urea, SGOT and SGPT levels, blood was taken on day 8 (H8). Uric acid level measurement using Easy Touch Multi Check. Creatinine, urea, SGOT and SGPT levels in serum blood were measured using Mindray BC-2800 hematology analyzer according to the device's instructions for use.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism with the one-way analysis of variance and Duncan's post hoc test. Uric acid level data on H0 and H8 were also analyzed statistically using the paired t-test. The significance was verified at $p < 0.05$, and measurements were indicated as mean ± standard error of the mean.

Result and Discussion

This study used hantap leaf extract obtained by maceration and obtained a yield of 5.11%. The results of phytochemical screening showed the presence of alkaloids, flavonoids, saponins, gallic tannins and steroids compounds. The results obtained are in line with previous research with the presence of this group of compounds (Yuliet, et al., 2023).

Testing the effects of hyperuricemia with ethanol extract of hantap leaves induced by chicken liver juice, which can increase uric acid levels in the blood due to its relatively high purine (xanthine) content that triggers uric acid formation with the presence of the xanthine oxidase enzyme (Karyadi et al., 2023). Additionally, potassium oxonate is used as an additional inducer, functioning as a uricase enzyme inhibitor. The inhibition of uricase by potassium oxonate causes the accumulation of uric acid that cannot be eliminated through urine (Wen et al., 2020). In most mammals, including rats, the uricase enzyme converts uric acid into more water-soluble allantoin. Uric acid will accumulate and not be eliminated in the form of urine due to the inhibition of the uricase enzyme by potassium (Roman, 2023).

Based on Figure 1 and Table 1 the uric acid levels before induction (H0) show no significant differences across all groups. This indicates that the uric acid levels of all test animals on day 1 before induction were in a normal state. Based on the results of uric acid levels on day 8, the significant rise in the negative control group confirms the induction method's efficacy in increasing uric acid levels. Increased uric acid levels in the negative control group by 74.2%. In the positive control group (Allopurinol), EEDH at doses of 200 mg/kg BW and 400 mg/kg BW showed significantly different results from the negative control, indicated by a decrease in uric acid levels. The administration of the extract at a dose of 100 mg/kg BW did not show a significant difference from the negative control. This indicates that the 100 mg/kg BW dose of the extract was not effective in reducing uric

acid levels compared to EEDH at doses of 200 mg/kg BW and 400 mg/kg BW.

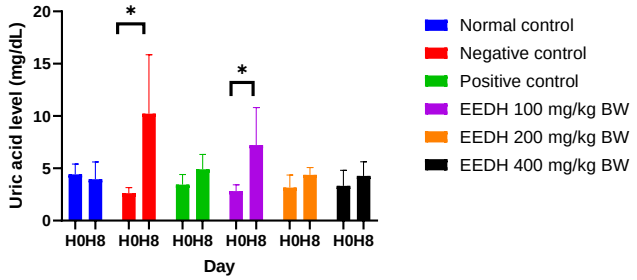

Figure 1. Effects of Hantap leaf extracts on serum uric acid levels in hyperuricemic rats. (*) P < 0.05 versus H0

Table 1. Mean Uric Acid Levels in Hyperuricemia Model Rats

Group	Uric acid levels (mg/dL)	
	H0	H8
Normal control	4.42 ± 0.44	3.96± 0.73[a]
Negative control	2.64 ± 0.24	10.22± 2.52[b]
Positive control	3.44 ± 0.43	4.9± 0.64[a]
EEDH 100 mg/kg BW	2.82 ± 0.27	7.22± 1.61[ab]
EEDH 200 mg/kg BW	3.16 ± 0.55	4.38± 0.31[a]
EEDH 400 mg/kg BW	3.32 ± 0.66	4.28 ± 0.60[a]

H0: rat uric acid levels before induction and treatment H8: rat uric acid levels after induction and treatment
Different alphabets indicate significant differences between treatment groups (P<0.05)

Increased blood uric acid levels can cause urate crystals in the kidneys. Elevated uric acid levels also contribute to the development and progression of kidney dysfunction (Liu et al., 2018). The kidneys excrete about two-thirds of uric acid. Uric acid is filtered, reabsorbed, and secreted in the proximal tubule. Chronic elevation of uric acid levels leads to kidney dysfunction. Hyperuricemia causes damage to the afferent arteriole, resulting in inadequate vasoconstriction, which leads to glomerular hypertension. Uric acid directly induces cell senescence and apoptosis in human endothelial cells through the local activation of oxidative stress and the renin-angiotensin system (RAS). Additionally, uric acid is a byproduct of xanthine oxidase, which transfers electrons to oxygen, generating oxidative stress and potentially causing cellular damage (Isaka et al., 2016). Creatinine and urea examinations can be used as one of the parameters to assess normal kidney function (Treacy et al., 2019). Based on the statistical analysis of creatinine and ureum levels presented in Table 2, the negative control showed significant differences with positive control, EEDH doses of 100 mg/kg BW, EEDH doses of 200 mg/kg BW, and EEDH doses of 400 mg/kg BW, which indicative of serious impairment of kidney injury in negative control.

Furthermore, EEDH at different doses significantly reduced creatinine levels by 39.62% (100 mg/kg BW), 37.74% (200 mg/kg BW) and 41.51% (400 mg/kg BW), respectively, and urea levels by 14.69% (100 mg/kg BW), 29.96% (200 mg/kg BW) and 17.47% (400 mg/kg BW), respectively, indicating some protective effects on renal function. The positive control allopurinol also showed a decrease in creatinine and urea levels of 22.64% and 21.43% respectively, which was not significantly different compared to the group given EEDH. Hantap leaf extract has the potential to treat hyperuricemia and improve kidney function due to its good xanthine oxidase inhibitor and antioxidant activity. Previous research has demonstrated that the antioxidant activity of hantap leaf ethanol extract is classified as very strong, with an IC_{50} value of 6.48 ppm (Cahyani et al., 2017). The optimal dose of hantap leaf extract is 200 mg/kg BW. A study by Xiao et al., 2021, also showed that resveratrol at doses of 50 and 100 mg/kg BW can reduce creatinine, urea, and uric acid levels. Additionally, resveratrol exhibited clear anti-inflammatory and antioxidative effects in hyperuricemic rats, suggesting that resveratrol may protect against hyperuricemic nephropathy by regulating the inflammatory and oxidative response.

SGOT and SGPT are biomarkers that can indicate hepatocyte damage (Chinnappan et al., 2023). Uric acid is known as a hepatotoxic agent that can cause inflammation and inflammatory tissue damage. Hyperuricemia is known to be one of the main causes of hepatocyte injury so that uncontrolled hyperuricemia will cause liver damage. Uncontrolled hyperuricemia causes injury to hepatocytes, which are the main site of uric acid metabolism, which will cause the formation of scar tissue in the liver structure (Sari et al., 2020; Yen et al., 2022).

This study found that there was a significant difference in serum SGOT and SGPT levels between the normal control group and the negative control group where the average SGOT and SGPT values in the group of rats induced with uric acid were significantly higher than in the group of rats without uric acid induction (negative control). These results indicate that uric acid induction can cause an increase in SGOT and SGPT levels which are markers that indicate liver damage. Uric acid stimulates an increase in the metabolism of reactive oxygen species (ROS) and the activation of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase), which produces superoxide radicals and the NOX4 subunit. These molecules can significantly reduce the mitochondrial membrane potential in hepatocytes and induce lipid accumulation as well as liver fibrosis. Hepatocyte damage can trigger an increase in SGOT and SGPT enzymes (Sari et al., 2020).

Table 2 shows that there is a significant difference in SGOT and SGPT levels in the negative control group with the treatment group at all doses of Hantap leaf extract and positive control. Where serum SGOT and SGPT levels in the positive control group and the EEDH group are lower than the negative control group. This indicates that there is an improvement in the functional status of the liver by administering Hantap leaf extract, indicated by a decrease in SGOT and SGPT levels. The previous study using leaf extract from different species but still within the same genus, *Sterculia diversifolia*, showed hepatoprotective effects at doses of 150 and 300 mg/kg body weight. Therefore, the leaf extract of Hantap could be a source of active compounds with potential hepatoprotective properties in hyperuricemia conditions (Rabbi et al., 2021).

Table 2. Blood Biochemistry of Hyperuricemic Rats

Group	Creatinine (mg/dL)	Ureum (mg/dL)	SGOT (Unit/L)	SGPT (Unit/L)
Normal control	0.40 ± 0.05^{ab}	34.27 ± 3.51^{a}	197.13 ± 14.42^{a}	56.83 ± 0.57^{a}
Negative control	0.53 ± 0.11^{b}	45.4 ± 2.66^{b}	262.60 ± 6.74^{b}	80.60 ± 7.76^{b}
Positive control	0.41 ± 0.02^{ab}	35.67 ± 2.39^{a}	228.50 ± 8.40^{ab}	71.96 ± 4.73^{ab}
EEDH 100 mg/kg BW	0.32 ± 0.04^{a}	38.73 ± 0.97^{ab}	240.63 ± 8.71^{ab}	73.60 ± 4.16^{ab}
EEDH 200 mg/kg BW	0.33 ± 0.01^{a}	31.8 ± 1,14^{a}	195,93 ± 21.11^{a}	80.16 ± 7.98^{b}
EEDH 400 mg/kg BW	0.31 ± 0.01^{a}	37.47 ± 1.34^{a}	209,56 ± 16.68^{a}	76.00 ± 8.17^{ab}

Different alphabets indicate significant differences between treatment groups (P<0.05)

The obtained results demonstrate the hepatoprotective effect of Hantap leaf ethanol extract by reducing oxidative stress and inflammatory biomarkers through an inhibitory mechanism on XO formation, leading to a decrease in uric acid levels. By inhibiting XO formation, the generation of ROS is also hindered, thereby minimizing liver damage.

Allopurinol is a xanthine inhibitor that has the potential to combat free radicals and reduce increased oxidation levels. Additionally, allopurinol can improve kidney and liver function (Glal et al., 2024; Korsmo et al., 2024). In this study, allopurinol has been proven to reduce levels of uric acid, creatinine, urea, SGOT, and SGPT, while hantap leaf extract can replace the role of allopurinol as an XO inhibitor through phenolic and flavonoids.

Previous studies have proven the presence of the highest compound content in hantap leaf extract, namely tannins, alkaloids, and flavonoids. The results of identification with LC-MS/MS revealed that there were at least 5 compounds, including 2 flavonoids, specifically 5,7-dihydroxy-3-(4'-hydroxy benzyl) chromone and kaempferide-3-O-α-L-rhamnosyl-7-O-α-L-rhamnoside (Yuliet et al., 2023). The ability of hantap leaf extract to reduce uric acid levels and act as a neuroprotective and hepatoprotective agent is due to the presence of these compounds with high antioxidant activity which can prevent oxidative stress activity in kidney and liver cells (Kumar & Nayak, 2020; Sharma et al., 2021).

The limitation of this study is that no histopathological study was conducted to directly observe the structural damage and repair of the kidneys and liver after the intervention. Future studies are needed to clarify the mechanism of action as a neuroprotectant and hepatoprotective agent in hyperuricemia conditions.

Conclusion

In conclusion, the present study demonstrated that Hantap (Sterculia *coccinea* Jack) has uric acid-lowering effects in hyperuricemic rats, and its mechanism of action may be related to inhibiting the activity of xanthine oxidase. Hantap leaf extracts were also found to be effective in protecting hepatic and renal tissue against chicken liver juice and potassium oxonate-induced damage as the hantap leaf extracts showed lower levels of creatinine, ureum, SGOT, and SGPT. Our findings support the use of this hantap as an alternative therapy for hyperuricemia. SGOT, and SGPT. Our findings support the use of this Hantap as an alternative therapy for hyperuricemia. Further extensive studies are necessary to validate the findings. A deeper understanding of the molecular mechanisms behind Hantap's anti-hyperuricemic potential will clarify its mechanism of action and interactions with cell.

Author Contributions

Conceptualization and methodology, Yuliet; software, Khildah K; validation, Yuliet.; formal analysis, Yuliet; investigation, Rhizky SA, Miranti, Ni Luh Rindiani, Marzelany MS; writing—original draft preparation, Yuliet and Khildah K; writing—review and editing, Yuliet. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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