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Original Article

Analysis of The Effectiveness Combination *Allium Ascalonicum L.* And *Zingiber Officinale Var. Rubrum* Extracts On Uric Acid Levels In Hyperuricemic *Rattus Norvegicus*

[1]Deinike Wanita Marwan, [2]Bimby Irenesia, [3]Evy Eryta, [4]Wiwi Sartika, [5]Randhy Aflah

[1,2]*Departement of Biomedicine, Faculty of Medicine, Universitas Abdurrab, Pekanbaru, Indonesia*
[3]*Departement of Clinical Sciences, Faculty of Medicine, Universitas Abdurrab, Pekanbaru, Indonesia*
[4]*Department of Midwifery, Faculty of Pharmacy and Health Sciences, Universitas Abdurrab, Pekanbaru, Indonesia*
[5]*Undergraduate Medical Student, Faculty of Medicine, Universitas Abdurrab, Pekanbaru, Indonesia*

E-mail Corresponding: ***deinikemarwan@univrab.ac.id***

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ABSTRACT

Background : Hyperuricemia is an increase in uric acid levels caused by increased uric acid metabolism (overproduction), decreased uric acid excretion through urine (underexcretion), or a combination of both. In Indonesia, the average age of occurrence is younger compared to Western countries, with approximately 32% of hyperuricemia cases occurring under the age of 34. The long-term and excessive use of medication can lead to toxic side effects. Previous studies have indicated that certain plants have effects in lowering uric acid levels, such as shallots (Allium ascalonicum L.) and red ginger (Zingiber officinale var. rubrum). This research aims to analyze the effectiveness of the combined extract of Allium ascalonicum L. and Zingiber officinale var. rubrum in reducing uric acid levels in male white rats induced with potassium oxonate.

Method : This study employed an experimental Pre-Post Test Control Group Design using male white rats divided into five groups, including negative and positive controls. The treatment groups received varying combinations of red ginger and shallot extracts. Hyperuricemia was induced using potassium oxonate at a dose of 250 mg/kg BW. Uric acid levels were measured using a multiparameter uric acid test strip. The extract combinations were administered orally for 7 consecutive days. Statistical analysis was conducted using One-Way ANOVA to assess differences in uric acid levels before and after treatment across the groups. A p-value of <0.05 was considered statistically significant.

Result : The One-Way ANOVA test showed a p-value <0.05, indicating a statistically significant reduction in uric acid levels. The most effective dose was the combination of 450 mg red ginger extract and 150 mg shallot extract, which showed the highest and most significant reduction in uric acid levels.

Conclusion : The combination of shallot and red ginger extracts is effective in reducing uric acid levels in hyperuricemic rats.

INTRODUCTION

Uric acid is the final product of purine metabolism in the body. According to research, 90% of uric acid is the result of purine catabolism, which is assisted by the enzymes guanase and xanthine oxidase. Uric acid is carried to the kidneys via the bloodstream to be excreted with urine, if there is a disruption in the elimination of uric acid by the kidneys due to reduced secretion of uric acid through the renal tubules, an increase in uric acid levels in the blood will occur[1,2]. Hyperuricemi is an excess of uric acid in the blood. Hyperuricemia causes uric acid crystal accumulation in a bowl. This condition generates a pain which is known as gout.[3-5]

In the population of gout patients, nearly 90% of hyperuricemia is caused by decreased uric acid excretion.[6] In the United States, hyperuricemia is most commonly found in men over the age of 34, with a prevalence of 5.9% (6.1 million) in men, compared to 2.0% in women. Hyperuricemia affects 3.9% of the adult population in the United States (8.3 million). In Indonesia, the prevalence is estimated at 13 per 10,000 people, and this prevalence increases with age. It is also notable that hyperuricemia in Indonesia tends to occur at younger ages compared to Western countries, with about 32% of hyperuricemia cases occurring in individuals under 34 years old.[7,8] The prevalence of hyperuricemia is rising, affecting 43.3 million (21%) adults. In Indonesia, 32% of gout cases occur in individuals under 34 years old, and 68% occur in individuals over 34 years old. According to the World Health Organization (WHO) data from 2015, the prevalence of gout cases has doubled from 1990 to 2010. In the United States, gout affects 8.3 million (4%) adults. Data from the Health Department of Pekanbaru shows that gout arthritis is among the top 10 most common diseases in public health centers, with 8,449 reported cases.[6,9]

The first-line medication used to help lower uric acid levels is allopurinol. Allopurinol is a uricosuric drug commonly used to reduce uric acid production by inhibiting the activity of the enzyme xanthine oxidase (XO).(10) However, prolonged excessive use of allopurinol can lead to toxic side effects such as high blood pressure, hypersensitivity reactions, kidney damage, and gastrointestinal disturbances.[6,11,12] In some hyperuricemia patients, the risk of hypertension is present in 25% of untreated patients, 50% of patients using diuretics, and over 75% of patients with malignant hypertension. Hypertensive patients with hyperuricemia have a 3-5 times higher risk of coronary or cerebrovascular diseases compared to hypertensive patients with normal uric acid levels. The kidneys play a crucial role in maintaining uric acid metabolism balance. Hyperuricemia is caused by inadeniquate renal excretion in about 90% of cases, while excessive production accounts for only 10%. The kidneys eliminate about two-thirds of the uric acid produced daily, with the remaining third excreted via the digestive system. About 90% of the filtered uric acid load is reabsorbed by the renal proximal tubules. The reabsorption of uric acid in the kidneys involves several transporters, such as urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9), whose function can be influenced by various factors, including genes, medications, elevated serum lead levels, and concentrations of lactate or ketones. An imbalance between uric acid production and elimination, particularly reliant on renal excretion, leads to hyperuricemia.[13]

The contents of *Allium ascalonicum L.*, including flavonoids, saponins, tannins, and allicin, possess therapeutic properties as antioxidants and inhibitors of xanthine oxidase activity. Xanthine oxidase is the enzyme responsible for uric acid formation, thus inhibiting uric acid production.[11,14] Additionally, these compounds can bind bile acids and increase bile acid excretion in feces, lowering cholesterol in plasma. Red ginger (*Zingiber officinale var rubrum*) is a plant from the Zingiberaceae family, containing therapeutic compounds such as flavonoids, alkaloids, terpenoids, and phenolics. Furthermore, ginger extract, rich in gingerol, has properties that help lower blood uric acid levels and possess anti-inflammatory effects.[1,12,15,16]

Based on tests on the uric acid-lowering activity of *shallots* and red ginger extracts, it is possible to combine these two plant extracts to enhance the effectiveness of uric acid therapy and demonstrate the advantages of herbal-based medicine products. This study aims to determine the effects of shallots (*Allium ascalonicum L.*) and red ginger (*Zingiber officinale var rubrum*) extracts on the reduction of uric acid levels in white rats induced with potassium oxonate.

Therefore, an alternative treatment using natural substances to help control uric acid levels in the body is needed besides allopurinol. Some plants that can be used to regulate uric acid levels in the body include *shallots* and red ginger. Shallots (*Allium ascalonicum L.*) is rich in flavonoids, with approximately 415-1917 mg of flavonoids in 1 kg of shallots. According to Murota and Terao, some of the therapeutic properties of flavonoids function as antioxidants and inhibitors of xanthine oxidase activity, which is responsible for the formation of uric acid, thus hindering uric acid production. Red ginger is a plant from the Zingiberaceae family, containing therapeutic compounds such as flavonoids, terpenoids, and phenolics. Moreover, ginger extract, rich in gingerol, has properties in lowering blood uric acid levels and possesses anti-inflammatory effects[17].

Hyperuricemia, defined as serum uric acid levels exceeding 6.8 mg/dL, is a prevalent metabolic disorder associated with gout, hypertension, and cardiovascular diseases.[13] The condition arises primarily due to impaired renal excretion of uric acid, accounting for nearly 90% of cases, while excessive production accounts for the remaining 10%.[6] In Indonesia, the incidence of hyperuricemia is increasing, affecting younger age groups compared to Western populations, and gout ranks among the top 10 diseases encountered in public health centers. Currently, allopurinol**,** a xanthine oxidase inhibitor, remains the first-line treatment. Although effective, its long-term use has been associated with significant adverse effects, such as hypersensitivity reactions, nephrotoxicity, and gastrointestinal disturbances.[6,7] These risks highlight the need for safer, natural alternatives that are both accessible and effective.

Several medicinal plants have been studied for their uric acid-lowering properties. *Allium ascalonicum L.* (shallots) contains flavonoids, saponins, tannins, and allicin — compounds known for their antioxidant properties and their ability to inhibit xanthine oxidase, the key enzyme in uric acid synthesis. Similarly, *Zingiber officinale var. rubrum* (red ginger) contains gingerol, flavonoids, and phenolics, which are reported to exhibit uricosuric and anti-inflammatory effects.

Hyperuricemia and gout have become increasingly prevalent both globally and in Indonesia. The World Health Organization (WHO) reported that the prevalence of gout cases doubled from 1990 to 2010. In the United States alone, gout affects around 8.3 million adults, accounting for 4% of the population. In Indonesia, 32% of gout cases occur in individuals under the age of 34, and 68% occur in individuals above 34 years old.[7] Conventional pharmacologic treatments, such as allopurinol a xanthine oxidase inhibitor are widely used as first-line therapy to lower uric acid levels.[20]

However, prolonged use of allopurinol is associated with adverse effects including hypersensitivity reactions, nephrotoxicity, gastrointestinal disturbances, and elevated blood pressure. These complications are reported in up to 25% of untreated patients, 50% of patients using diuretics, and over 75% of patients with malignant hypertension. Additionally, hyperuricemic patients with hypertension have a 3–5 times higher risk of coronary or cerebrovascular diseases than those with normal uric acid levels.[6] Given these challenges, the development of alternative, safer, and more accessible therapies is urgently needed. One promising avenue is the use of plant-based therapies derived from local medicinal plants. Shallots (*Allium ascalonicum L.*) and red ginger (*Zingiber officinale var. rubrum*) contain bioactive compounds such as flavonoids, allicin, gingerol, alkaloids, and phenolics, which exhibit antioxidant, anti-inflammatory, and xanthine oxidase inhibitory effects. These properties enable them to reduce the synthesis of uric acid and potentially offer dual action through antioxidant protection and urate-lowering effects.[5-7] Flavonoids found in *Allium ascalonicum L.*, ranging from 415–1917 mg/kg, are known to inhibit xanthine oxidase, the enzyme responsible for converting hypoxanthine and xanthine into uric acid[1]

Meanwhile, gingerol-rich extracts from *Zingiber officinale var. rubrum* have shown uric acid-lowering and anti-inflammatory effects in various in vivo models.[6,7] These synergistic effects suggest that a combination of shallot and red ginger extracts may serve as a novel and promising phytotherapy for hyperuricemia management. This study is thus critical in evaluating the potential of shallot and red ginger extracts in reducing uric acid levels in hyperuricemic *Rattus norvegicus*. The findings may pave the way for the development of effective, low-toxicity herbal-based medications that are accessible and culturally acceptable, particularly in Indonesia, where traditional medicine remains an important part of healthcare.[1,6,8]

METHOD

This study employed an experimental Pre-Post Test Control Group Design using male white rats divided into five groups, including negative and positive controls. The combination of shallots and red ginger extracts, in concentrated form, is administered to the test animals via oral routes with varying concentrations: 70% shallots extract and 30% red ginger extract, 50% shallots extract and 50% red ginger extract, and 30% shallots extract and 70% red ginger extract, with a total dose of 600mg for each concentration group. The extraction is performed using the maceration method, and the macerated extracts are filtered, then evaporated and concentrated using a rotary evaporator under low pressure at 65°C to thicken the extract.

The study uses 30 male Wistar rats (Rattus norvegicus) aged 2-3 months, weighing 150-200g, in good health, active, and without deformities. The rats are adapted for 7 days and provided with food and water ad libitum. The rats are housed in plastic cages (20cm diameter), with bedding of sawdust. Six rats are placed in each cage, provided with food and water as needed, and their body weights are measured. On day 7 after adaptation, the rats are induced with potassium oxonate intraperitoneally. Then, the herbal extract combinations are administered for 14 days. On day 15, final uric acid levels are measured. Blood samples are collected from the tail vein, with 0.5-1 mL of blood drawn. Uric acid levels are measured using a multiparameter uric acid test strip.

This study is a true experimental research with a pre-test and post-test control group design. The study has received ethical approval from the Research Ethics Committee of Abdurrab University with the approval letter number NO. 025/KEP-UINVRAB/VI/2023. Statistical analysis is performed using SPSS 25.00. Univariate analysis is used to describe the characteristics of each variable, including independent variables (combination of shallots and red ginger extracts) and dependent variables (glucose levels in male Wistar rats with hyperglycemia induced by alloxan). One-way ANOVA is used to detect differences, and significant differences are further analyzed using the Bonferroni post-hoc test. A p-value of <0.05 is considered statistically significant.

RESULTS

The research was conducted at the Research & Innovation Laboratory of Abdurrab University using male white rats (*Rattus norvegicus*) of the Wistar strain, totaling 30 rats. The rats were divided into 5 groups, each consisting of 6 rats, and the test animals were screened beforehand according to the determined criteria. Extracts of red ginger and shallots that had been previously identified were then administered to the test animals at the specified doses for 14 days.

On the first day (pre-test), all groups of rats showed quite high uric acid levels, indicating that the induction of hyperuricemia was carried out evenly. The negative control group, which did not receive any treatment, had the highest average uric acid level of 8.38 ± 1.25 mg/dL, suggesting baseline hyperuricemic status. The positive control group, which received standard antihyperuricemic therapy (most likely allopurinol or a similar agent), showed a lower mean level of 6.90 ± 1.21 mg/dL, indicating partial efficacy even before repeated treatment administration. Variability among subjects within this group was moderate (SD = 1.21), suggesting some individual variation in uric acid response or metabolism. Among the experimental groups receiving combinations of *Allium ascalonicum* L. and *Zingiber officinale* var. *rubrum* extracts: 1). Experiment I showed a mean of 7.26 **±** 0.71 mg/dL (the most homogeneous group), 2). Experiment II had a slightly higher mean of 7.58 ± 1.04 mg/dL, 3). Experiment III showed a mean of 8.28 **±** 2.34 mg/dL, indicating the highest inter-individual variability (widest SD).

Table 1. Analysis of Uric Acid Levels in Rats Pre-test (Day 1)

Experiment groups	N	Minimum (mg/dL)	Maximum (mg/dL)	Mean (mg/dL) ± SD
Negative group	5	6.5	9.7	8.38± 1.25
Positive group	5	5.9	9.0	6.90 ± 1.21
Experiment I	5	6.5	8.2	7.26 ± 0.71
Experiment II	5	6.5	9.0	7.58 ± 1.04
Experiment III	5	6.4	11.9	8.28 ± 2.34

These values reflect the baseline status prior to treatment. The relatively high baseline uric acid levels in all groups confirm the model validity for evaluating antihyperuricemic effects. Natural products like *Allium* and *Zingiber* have been shown in previous studies to modulate xanthine oxidase activity and oxidative stress, which are involved in uric acid metabolism.

After 15 days of treatment The negative group paradoxically showed an average negative change (-5.32 ± 0.88 mg/dL**)**. This may reflect the use of delta values (change from baseline), not absolute values. The positive group showed significant reduction to 2.98 ± 0.41 mg/dL, consistent with expected pharmacological effects of uric acid-lowering agents (e.g., allopurinol) (4). Experiment II showed the greatest uric acid reduction among treatment groups (mean: 2.72 ± 0.63 mg/dL**)**, even lower than the positive control, suggesting superior therapeutic potential. Experiment I and III yielded mean values of 3.48 ± 0.65 mg/dL and 3.00 ± 0.90 mg/dL, respectively. The reduction across groups suggests that the combination of *Allium ascalonicum* and *Zingiber officinale* extracts may contribute to uric acid lowering, possibly via synergistic inhibition of xanthine oxidase and antioxidant pathways. This finding supports previous studies highlighting the potential of these plants as alternative or adjunct antihyperuricemic agents.(3)

Table 2. Analysis of Uric Acid Levels in Rats Post-test (Day 15)

Experiment groups	N	Minimum (mg/dL)	Maxiimum (mg/dL)	Mean (mg/dL) SD
Negative group	5	-6.3	- 4.3	-5.32 ± 0.88
Positive group	5	2.3	3.3	2.98 ± 0.41
Experiment I	5	2.6	4.4	3.48 ± 0.65
Experiment II	5	4.1	6.0	2.72 ± 0.63
Experiment III	5	2.0	4.3	3.00 ± 0.90

In Table 3 below, the uric acid levels in the experiment before and after treatment can be observed. The results show that the greatest reduction occurred in the positive group treated with allopurinol. Among the three groups treated with a combination of shallot and red ginger extracts, Treatment Group 1 (shallot 150 mg and red ginger 450 mg) experienced the most significant reduction in uric acid levels. Subsequently, Treatment Group 2 (shallot 300 mg and red ginger 300 mg) and Treatment Group 3 (shallot 450 mg and red ginger 150 mg) experienced the smallest reductions in uric acid levels.

The results obtained from the one-way ANOVA test indicated a p-value < 0.05, meaning there were significant differences between the groups compared. The test was then followed by a post hoc test, specifically the Bonferroni test, to determine which groups had significant differences (p < 0.05).

The negative group showed significant differences compared to the positive group, shallot 150 mg & red ginger 450 mg, shallot 300 mg & red ginger 300 mg, and shallot 450 mg & red ginger 150 mg. The positive group showed significant differences compared to the negative group and shallot 450 mg & red ginger 150 mg. Treatment Group 1 (shallot 150 mg & red ginger 450 mg) showed significant differences compared to the negative group, while Treatment Group 2 (shallot 300 mg & red ginger 300 mg) and Treatment Group 3 (shallot 450 mg & red ginger 150 mg) showed significant differences compared to the negative group, positive group, and Treatment Group 1.

Table 3. *Descriptive Analysis of the Difference in Uric Acid Levels in Rats*

Experiment groups	N	Mean pre-test (mg/dL)	Mean post-test (mg/dL)	Difference
Negative group	5	8.38	-5.32	- 3.06±1.20
Positive group	5	6.90	2.08	3.92±0.60
Experiment I	5	7.26	3.48	3.78±0.37
Experiment II	5	7.58	3.72	3.86±1.46
Experiment III	5	8.92	5.45	3.47±2.05

DISCUSSION

In this study, the rats were first adapted to their living environment in the animal house for one week. Screening was then conducted on the rats to determine whether the test animals had developed hyperuricemia at the outset. After being examined with a uric acid tool, the screening results showed that all rats met the inclusion criteria, indicating no initial increase in uric acid levels, making them suitable as samples in this study. This aligns with research by Rahayu et al. (2019), which stated that normal uric acid levels in rats range between 1.11–5.37 mg/dL.

The samples were induced with potassium oxonate, with each sample receiving a dose of 4.5 mg according to the predetermined conversion. Previous research by Haryadi et al. (2020) stated that potassium oxonate is injected into the samples, and an increase in uric acid levels occurs after 24 hours. One day later, uric acid levels were checked, and it was found that all rats were in a hyperuricemic state. On the same day, treatment was initiated by administering the combination extracts according to the prescribed doses.[1]

In previous research by Haryadi et al. (2020), uric acid levels were monitored for 21 days, with checks conducted weekly. In this study, data on uric acid levels before and after treatment showed that the quickest reduction occurred in the positive group treated with allopurinol, while the slowest reduction occurred in rats treated in Treatment Group 3 (shallot extract 450 mg and red ginger extract 150 mg). This is consistent with the findings of Haryadi et al. (2020), where the slowest reduction in uric acid levels occurred in treatments with higher shallot extract content than red ginger extract. The group that experienced the fastest reduction in uric acid levels was the group treated with a higher red ginger extract content than shallot extract.[1]

Based on the percentage of the average reduction in uric acid levels after treatment, the results, from fastest to slowest, were as follows: the positive group (allopurinol), Treatment Group 1 (shallot 150 mg & red ginger 450 mg), Treatment Group 2 (shallot 300 mg & red ginger 300 mg), and Treatment Group 3 (shallot 450 mg & red ginger 150 mg). This indicates that among the three combination extract treatments, the combination of shallot 450 mg and red ginger 150 mg was the most significant and effective in reducing uric acid levels in rats. The negative group was excluded because this group did not receive any treatment.

Based on the One-Way ANOVA test, there were significant differences in uric acid levels in rats between the pretest and posttest injections of potassium oxonate ($p < 0.05$), consistent with the findings of Haryadi et al. (2020). Potassium oxonate is a chemical compound that competitively inhibits the uricase enzyme, blocking the effect of liver uricase and excessively producing uric acid in the body, making it suitable as an inducer of hyperuricemia. Potassium oxonate increases uric acid production in the body, exceeding normal levels and causing hyperuricemia.[1]

Data analysis using One-Way ANOVA with Bonferroni indicated significant differences in uric acid reduction in rats before treatment ($p < 0.05$). The negative group showed significant differences compared to the positive group, shallot 30% & red ginger 70%, shallot 50% & red ginger 50%, and shallot 70% & red ginger 30%. For all other groups, significant differences were only found compared to the negative group, with no significant differences between other groups.

Data analysis using One-Way ANOVA with Bonferroni also showed that the negative group significantly differed ($p < 0.05$) from the positive group, shallot 30% & red ginger 70%, shallot 50% & red ginger 50%, and shallot 70% & red ginger 30%. The positive group significantly differed from the negative group, shallot 50% & red ginger 50%, and shallot 70% & red ginger 30%. The shallot 30% & red ginger 70% group significantly differed from the negative group and shallot 70% & red ginger 30%. The shallot 50% & red ginger 50% group significantly differed from the negative group. Similarly, the shallot 70% & red ginger 30% group significantly differed from the negative group, the positive group, and shallot 30% & red ginger 70%.

This indicates that a combination of shallot and red ginger extracts is effective in reducing uric acid levels, although it is not as optimal as using allopurinol.

Shallots and red ginger both contain active compounds known as flavonoids. Flavonoids reduce uric acid levels by inhibiting the activity of xanthine oxidase, which catalyzes the conversion of hypoxanthine to xanthine and then xanthine to uric acid, thus preventing excessive uric acid levels.[6,14] Other active compounds in shallots and red ginger, such as alkaloids, quercetin, and terpenoids, also contribute to reducing uric acid levels, working similarly to flavonoids.[17]

This study shows that administering the three combination extract treatments of shallots and red ginger positively impacts reducing uric acid levels in rats, even though their effectiveness varies. The most effective combination was shallot extract 30% and red ginger extract 70%, as it caused a drastic and effective reduction in uric acid levels in hyperuricemic rats compared to other treatments..

CONCLUSIONS

The administration of a combination of shallot and red ginger extracts has been proven effective in lowering uric acid levels in hyperuricemic rats. Among the tested combinations, the group receiving 30% shallot extract (150 mg) and 70% red ginger extract (450 mg) demonstrated a more significant reduction in uric acid levels compared to other combinations and the negative control group. This suggests a synergistic effect between the bioactive compounds present in both extracts, enhancing their antihyperuricemic properties. The findings highlight the potential of utilizing natural plant-based therapies as alternatives or complements to conventional treatments for hyperuricemia. The combination of shallot and red ginger extracts could offer a natural, cost-effective, and accessible means to manage elevated uric acid levels, especially in populations with limited access to standard pharmaceuticals. Moreover, the use of such herbal combinations may reduce the risk of side effects associated with synthetic drugs. In the future, further research is needed to elucidate the exact mechanisms by which the combination of shallot and red ginger extracts exerts its antihyperuricemic effects. Understanding the interaction between their bioactive compounds and metabolic pathways will provide deeper insights into their therapeutic potential. Determining the optimal ratios and dosages for maximum efficacy and safety is crucial. While the 30:70 combination showed promising results, exploring a broader range of ratios could identify even more effective formulations. Translating these findings from animal models to human subjects requires well-designed clinical trials to assess efficacy, safety, and potential side effects in humans. Ensuring consistency in the preparation and concentration of herbal extracts is essential for reproducibility and widespread application. Developing standardized extraction and formulation protocols will be a key step forward.

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