

ANALYSIS OF THE EFFECTIVENESS OF NATURAL INGREDIENTS IN ANTHYPERURICEMIA:REVIEW

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ABSTRACT

Introduction: Hyperuricemia is characterized by increased uric acid levels in the blood due to excessive production or impaired excretion. In Indonesia, the hyperuricemia rate reaches 18% of the total population. **Objective:** This study aimed to explore and analyze the potential of medicinal plants with antihyperuricemic activity in reducing uric acid levels in patients with hyperuricemia and experimental animals. **Materials and Methods** A total of 21 scientific articles were reviewed, focusing on the treatment of hyperuricemia using natural ingredients. Data were obtained from the Google Scholar and PubMed databases using keywords such as “hyperuricemia,” “medicinal plants,” and “natural therapy.” The inclusion criteria were articles published within the last 10 years that involved in vitro and in vivo models. **Results:** The review identified several natural ingredients, including turmeric, kepel leaves, and mangosteen peel, which demonstrated significant antihyperuricemic effects. These ingredients were effective in reducing uric acid levels in both animal and human studies. **Conclusion:** Natural ingredients show promising potential as alternative treatments for hyperuricemia by inhibiting xanthine oxidase activity. However, further clinical trials are required to validate these findings and support their application in therapeutic practice.

Keywords: Antihyperuricemia, Uric Acid, Natural Ingredients, Clinical Trials

INTRODUCTION

Hyperuricemia is a disease condition that is indicated by an increase in uric acid levels in the blood until they exceed normal levels, which is above 6.0 mg/dl in women and above 7.0 mg/dl in men. Under normal conditions, uric acid plays an important role in the body as an antioxidant. Meanwhile, when patients have hyperuricemia, plasma and extracellular fluid are saturated with uric acid. This condition occurs due to increased uric acid synthesis, decreased uric acid excretion by the kidneys, or both of these things occurring simultaneously. Hyperuricemia does not have significant symptoms, but when chronic complications occur, it can result in gouty arthritis, which is a condition in which the joints become inflamed due to the deposition of *Monosodium Urate* (MSU) crystals. This triggers an inflammatory response. Apart from that, when uric acid is excessive and then accumulates, it will cause damage to the joints and soft tissue which can trigger the condition of urate *nephrolithiasis* (kidney stones) with the risk of chronic kidney disease if proper treatment is not received (Yanti, 2010)

Based on information from the *Global Health Data Exchange* (GHDx) and the *World Health Organization* (WHO), in 2017, it was known that around 10-40% cases of hyperuricemia occurred worldwide. In Indonesia, the hyperuricemia rate reaches 18% of the

total population. This disease is triggered by increased uric acid levels, which can occur due to the influence of age, sex, body weight, congenital diseases in the form of impaired kidney function, and the food consumed, one of which is food with a high purine content, including offal, crab, spinach, and melinjo. This food is a type of food that is much loved by Indonesian people. Based on age and gender, this disease has an increased risk in men over 30 years of age and women over 50 years of age, or it can be seen that men have a higher risk than women. This phenomenon is related to the presence of estrogen in women, which can play a role in increasing uric acid excretion through the kidneys, so that uric acid levels in the body can be better controlled (Amal, 2021).

Therapeutic management of this disease is commonly achieved through the administration of synthetic drugs, such as allopurinol, which exerts its effects by inhibiting the activity of the xanthine oxidase (XO) enzyme. XO is an enzyme that causes high uric acid levels because its mechanism converts hypoxanthine into xanthine and produces the final product in the form of uric acid; therefore, the performance of this enzyme needs to be weakened to control uric acid levels in the body. However, despite this, this drug has side effects which are now increasingly recognized by the public as causing side effects in the form of skin allergies, headaches, liver and kidney damage, as well as triggering digestive tract disorders such as nausea and diarrhea. The high risk triggered by the consumption of synthetic drugs causes people to avoid using these drugs and choose to look for other alternatives that are based on natural ingredients, which are relatively safer, have fewer side effects, and can be used as guiding compounds for exploring new drugs (Nurliyamanda, 2022).

Based on the above description, hyperuricemia cannot be treated effectively and without causing side effects. Therefore, the author is interested in conducting a *narrative review* with the title "Analysis of the Effectiveness of Natural Ingredients in Antihyperuricemia" to explore information and data related to natural ingredients as antihyperuricemia and the effects of the best dose therapy to achieve the antihyperuricemia activity target.

RESEARCH METHOD

The research method used is a literature review of existing books and scientific publications. The approach chosen for this research is the *narrative review method*, in which the process of collecting material or discussion material is obtained using the basis of scientific publications and previous research that are related to this topic. Techniques or approaches are used to identify studies that describe a topic of interest. Information and previous studies were searched using the keywords hyperuricemia, antihyperuricemia drugs, and natural ingredients for lowering uric acid and obtained more than 50 of literature. In this study, 21 articles were reviewed based on existing problems. According to Melfianora, studies using this method can be used for a wider scope, which is not limited to references for the initial stages of preparing the research framework but can also be used to obtain data and information in research. The articles and materials to be studied in this *narrative review* were selected through the Google Scholar and PubMed platforms to filter articles published in the last decade. The data and information obtained will then be analyzed and linked back between one piece of literature and another to obtain further and clearer information and data regarding the problem being studied. This method allowed the author to compile and present the results of previous research.

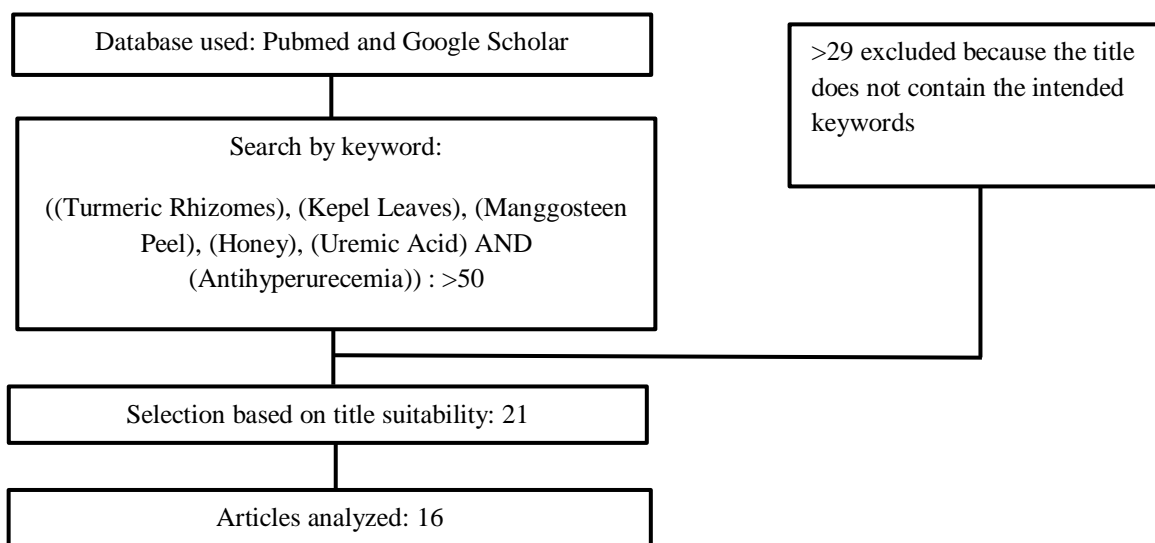


Figure 1. Flow of Article Search

RESULTS AND DISCUSSION

The research was conducted by identifying and analyzing information obtained from several literatures. Among the literature, it is known that the types of plants used as samples have proven anti-hyperuricemic activity using *in vivo observation methods*, namely 4 natural ingredients including turmeric rhizomes, kepel leaves, mangosteen peel, and pure honey. The following is an explanation of each natural material studied in this study.

Turmeric (*Curcuma domestica* Val) is a medicinal plant with antihyperuricemic activity. Turmeric contains the phytochemical *curcuminoid*, which acts as an antioxidant and has hypocholesteromic, cholagogum, choloretic, spasmolytic, antihepatotoxic, and anti-inflammatory properties; thus, it can relieve inflammation caused by uric acid deposits in the joints. The compounds in turmeric with anti-inflammatory effects are gingerol and shogaol, both of which can inhibit the activity of the *cyclooxygenase -2* (COX-2) enzyme. There are other ingredients including alkaloids and terpenoids which have antihyperuricemia activity due to their ability to inhibit the performance of the XO enzyme (Putri *et al.*, 2024),



Figure 2. Turmeric Rhizomes

Based on various studies that have tested the effectiveness of turmeric as an antihyperuricemia agent, it is known that turmeric rhizomes (*Curcuma domestica* Val) have antihyperuricemia activity. This is caused by the curcumin content in turmeric, which can inhibit Cyclooxygenase-2 (COX-2) activity. Therapy for patients with gouty arthritis is a combination of improved lifestyle and anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAID) and corticosteroids. Based on the various findings mentioned above, it can be concluded that turmeric has the potential as a hypouricemic agent that can be

used in pharmacological treatment to reduce uric acid levels in the body. Thus, turmeric can be one of the components in a hyperuricemia potion, which has the potential to reduce blood uric acid levels and is classified as practically non-toxic. This study provides a strong basis for further research into the potential of turmeric in the management of hyperuricemia in humans

Studies on the use of kepel leaves have also been conducted. Kepel (*Stelechocarpus burahol*) is a plant whose fruit is commonly used in traditional medicine. The chemical content of kepel fruit, such as flavonoids and other bioactive compounds, has attracted attention in research as a potential antihyperuricemia agent (Putri *et al.*, 2024).



Figure 3. Kepel Leaves

Based on various previous studies, kepel leaves (*Stelechocarpus burahol*) showed positive results for antihyperuricemia activity. Kepel leaves contain chemicals such as flavonoids and other bioactive compounds that have the potential to act as antihyperuricemia agents. The various studies mentioned above show the ability of kepel leaves as an antihyperuricemia compound, although when tested separately, they show low ability. However, despite this, kepel leaves combined with other ingredients, such as allopurinol, have proven to be more effective as an antihyperuricemia compound. Kepel leaves contain n-hexane, ethyl acetate, and flavonoids, which reduce urea levels in the blood. Flavonoids play a role in inhibiting the inhibitory activity of XO, leading to significant changes in antihyperuricemia by reducing uric acid levels.

Another natural ingredient that has the potential to act as an antihyperuricemia is mangosteen peel extract, which is the skin of the mangosteen fruit that contains xanthonenes, flavonoids, and tannins. This triggers the potential for anti-hyperuricemia because xanthonenes are high-level antioxidants, which can treat cells damaged by free radical oxidation, as an inhibitor of the aging process, and prevent generative diseases (Dira, Eka, Fitrianda, 2014).



Figure 4. Mangosteen Peel
(References: Primary Data)

Based on various previous studies, mangosteen peel has shown positive results as an antihyperuricemia agent. Mangosteen rind contains xanthonenes, flavonoids and tannins. In previous research that was carried out, one of the antihyperuricemia activity tests was carried

out by calculating the percentage of XO enzyme inhibition for further comparison with allupurinol which acts as a standard inhibitor of the xanthine oxidase enzyme. EKM showed results in the form of large inhibitory power (49.231%) and from the research results it was found that mangosteen peel extract significantly reduced uric acid levels in test animals (rats) compared to the negative control group. Analysis also revealed that granules prepared from the ethanol extract of mangosteen peel contained a total of 4.024 mg xanthonenes per 50 units of extract, indicating the potential of mangosteen peel extract as an antihyperuricemia agent that can be further developed.

The last natural ingredient studied in this research as an antiperuricemia is pure honey, combined with other natural ingredients. Honey contains various free radical-fighting substances, including glucose, *sucrose*, and *maltose*. If this content is present in adequate amounts, it can remove uric acid levels in the body that exceed its capacity and has the property of eliminating excess purine in the blood and destroying crystals in the joint area (Klionsky et al., 2025).



Figure 5. Honey

Based on various previous studies regarding the effectiveness of honey as an antihyperuricemic combination ingredient, it is known that the addition of honey shows positive results in reducing uric acid levels. Honey contains various substances that can ward off free radicals, such as *glucose*, *sucrose*, and *maltose*. This substance, if administered at the correct dosage, can play a role in removing excess uric acid levels in the body (Morales et al., 2023). Honey is a natural ingredient that can be combined to reduce uric acid levels. Studies have shown that there is significant activity in reducing blood uric acid levels when using honey. This ingredient also does not show any side effects for sufferers, so it can be used as a combination ingredient with antihyperuricemia agents from other natural ingredients discussed in this *narrative review*.

Natural ingredients can be used as antihyperuricemic agents either alone or in combination with other natural ingredients. **Table I** shows the activity of natural ingredients observed in this study in their role as alternative antiperuricemia drugs.

Table I. Activity of Natural Ingredients (Turmeric Rhizome, Kepel Leaves, Mangosteen Peel, Honey) as Anthyperuricemia ingredients from Various Previous Research

Natural Ingredients	Method	Treatment	Mechansim	Ref.
Single Ingredient (In Vivo)				
Turmeric Rhizome	In Vivo (mice, eye inflammation)	Healthy control (K-), positive control infected with <i>S. aureus</i> (K+), group of mice treated with 5% turmeric extract (K1); 10% (K2); 20% (K3); and <i>chloramphenicol</i> 0.25% (KP). Mice's eyes were infected for 3 days and treated for 7 days to be taken and observed on the 19th day	20% turmeric extract reduced inflammatory cells → potential to treat inflammation in gouty arthritis	(Bagad <i>et al.</i> , 2013)
	In Vivo (patients with gouty arthritis)	Turmeric essential oil at a dose of 25 mg/kg BW was given regularly for 1 full week to the test samples	Significant reduction in blood urea levels	(Fahryl <i>et al.</i> , n.d.)
	Clinical (55 subjects)	The first group consumed a decoction of hyperuricemia herb for 28 days. The second group consumed herbal tablets at a dose of 3x2 tablets regularly for the same duration.	Both treatments equally reduced uric acid	(Putri <i>et al.</i> , 2024)
	In Vivo (mice, high purine diet)	Samples were divided into treatment (P1) and control (K) groups. P1 was given 25 mg/kg BW/day essential oil capsules regularly for 7 days and K was given 150 mg/kg non-steroidal anti-inflammatory drugs BB/day.	Reduced blood urea & TNF- α levels	(Yanti, 2010)
Mangosteen Peel Extract	In Vivo (rats, pulp inflammation)	Negative control, mangosteen pericarp extract treatment group, and calcium hydroxide treatment group (positive control). Samples were analyzed histopathologically on D+1, 3, 5, and 7.	Reduced neutrophils, anti-inflammatory effect	(Gigi <i>et al.</i> , 2022)
	In Vivo (mice, hyperuricemia)	Mangosteen peel extract with different doses , P1 Control; P2 0.2 g/kg BW ; P3 0.4 g/kg BW ; and P4 0.6 g/kg BW in male mice and their uric acid levels were observed.	Lowest uric acid in 0.6 g/kg BW group	(Fitri <i>et al.</i> , 2017)
	In Vivo (rats, extract + granules)	Negative control group, group positive control with allopurinol as standard, and 2 treatment groups with doses of mangosteen peel extract of 40 and 80 mg/kg BW , respectively . After treatment, uric acid levels were measured on days 1, 7, and 14 to see the effect on reducing uric acid levels.	Both doses reduced uric acid; xanthones active	(Nurhidayah <i>et al.</i> , 2022)
Honey	Clinical (16 gout patients)	This research has research <i>design quasi e x experimental design</i> , namely <i>post test 2 groups</i> so that the difference in uric acid levels before and after consume honey. Data analysis was presented	Significant reduction in uric acid (1.78 vs. 0.77)	(Laratmase <i>et al.</i> , 2021)

		univariately and bivariately using the independent T test.		
Mixed Ingredients (In Vivo)				
Turmeric Rhizome	Clinical (15 elderly)	Giving a decoction of traditional therapy , namely Ginger Rhizome (<i>Z. officinale roscoe</i>), Turmeric (<i>C. Domestica</i>) and Lemongrass (<i>S. citratus</i>).	Decreased uric acid, but effect varied	(Manangin, 2020)
	In Vivo (mice)	1. control lozenges without extract 2. control allopurinol suspension 3. L lozenges solution of kepel leaf extract at a dose of 100 mg/KgBW 4. Kepel leaf extract lozenges solution at a dose of 150 mg/KgBW 5. L lozenges solution of kepel leaf extract dose 200 mg/KgBW All groups were induced by caffeine for 6 days orally. Observations on days 9, 12, and 15.	Reduced uric acid by 81–89%	(Ibrahim, 2017)
Kepel Leaves	In Vivo + In Vitro (rats, XO assay)	6. Kepel leaf extract fractionated with n - hexane and ethyl acetate. Inhibitory fraction activity XO in model mice hyperuricemia was calculated uric acid levels with method <i>ultraviolet-visible spectrophotometry</i>	n-hexane fraction showed weak XO inhibition	(Latief <i>et al.</i> , 2021)
	In Vivo & In Vitro (rats, XO inhibition)	7. In vivo test ethyl acetate subfraction given orally and directly to mice taken every 1, 2 , and 3 hours to be frozen at room temperature and centrifuged 10,000 rpm for 7 minutes for got the serum which will be tested with <i>enzymatic colorimetric</i> . In vitro , 1 ml fraction plus 0.9 ml phosphate buffer, 0.1 ml XO and Xanthine 0.15 mM later Incubate 30 minutes , 25 °C. Added 1 ml 1 N acid hydrochloride and absorbance measured 287 nm with a spectrophotometer. Fraction with different concentrations dissolved in DMSO	Reduced uric acid in vivo; low XO inhibition in vitro	(Sunarni <i>et al.</i> , 2017)
Mangosteen Peel Extract	In Vitro (XO inhibition)	1. 0.108 mg/day astaxanthin and EKM 800 mg/kgBW/day 2. 0.216 mg/day astaxanthin and EKM 800 mg/kgBW/day 3. 0.432 mg/day astaxanthin and EKM 800 mg/kgBW/day 4. Positive control with celecoxib 18 mg/kgBW/day	IC50 = 8.31 µg/mL; inhibited XO activity.	(Dira, Eka, Fitrianda, 2014)

			5. Negative control with CMC 1 mL.		
	Clinical (32 gout patients)		Respondents checked uric acid levels before and after consuming honey pineapple juice with <i>Easy Touch GCU digital</i> .	Uric acid decreased (8.3 → 6.7 mg/dl)	(Salsa, 2021)
Honey	Clinical (44 patients)		Design experimental research with <i>Quasi Experiment Design</i> . The dose of roselle and honey soaking given to the treatment group was 74 mL.	Significant reduction in uric acid ($p < 0.05$)	(Ibrahim, 2017)
	Clinical (9 hyperuricemic volunteers)		100 mL of herbal medicine X containing oxygen, honey nectar, palm sugar, Mahkotadewa extract; Tapak Liman; and <i>Sida rhombifolia</i> , as well as Tempuyung leaf extract. Measurement of blood uric acid levels during and 1 hour after consuming 2 tablespoons of herbal medicine X, using a <i>portable measuring strip test</i> .	No significant change in uric acid	(Harmanto et al., 2019)
Single Ingredient (In Vitro)					
	In Vivo & In Vitro (rats, XO inhibition)		Model mice given ethanol extract of <i>S. burahol</i> , <i>A. muricata</i> , and <i>A. reticulata</i> with dose 75 mg/kgBB rats and comparison allopurinol 10 mg/kgBB rat. Blood the mice were then taken within 1 hour, 2 hour, and 3 hours after administering medication then centrifuged at 10,000 rpm, 7 minutes	Reduced uric acid in vivo; low XO inhibition in vitro	(Sunarni et al., 2017)
Kepel Leaves	In Vivo & In Vitro (rats, XO inhibition)		<i>S. burahol</i> leaf powder was extracted with ethanol, then fractionated using the liquid-liquid extract method with n-hexane and ethyl acetate. The rat model was induced with potassium oxonate intraperitoneal. The activity of these fractions towards XO inhibition was measured by measuring uric acid formation by ultraviolet-visible spectrophotometry after incubation with XO.	Reduced uric acid in vivo; low XO inhibition in vitro	(Sunarni et al., 2017)
Mixed Materials (In Vitro)					
	In Vitro		This is a cross-sectional retrospective study with <i>purposive sampling</i> through analysis of medical records of patients with hyperuricemia who consumed 3 ingredients, namely:	Significant reduction in blood urea levels.	(Sonia, 2020)
Kepel Leaves and Turmeric Rhizome			<ul style="list-style-type: none"> • Secang bark (<i>C. sappan</i>), tempuyung herb (<i>S. arvensis</i>), kepel leaves (<i>S. burahol</i>) with 72 recipes (60%) 		

		<ul style="list-style-type: none"> • Javanese chilies (<i>P. retrofactum</i>), spoon leaves (<i>P. major</i>), celery (<i>A. graveolens</i>) with 36 recipes (30%) • Bolong grass (<i>E. debille</i>), ginger (<i>C. xanthorizza</i>), turmeric rhizome (<i>C. domestica</i>) with 12 recipes (10%). 	
Mangosteen Peel Extract	In Vitro (XO inhibition)	<ul style="list-style-type: none"> • The concentrations used for ethanol extract of mangosteen rind are 8, 12, 16, 20, 24 and 28 µg/mL. • Allopurinol 1,2,4,6,8, and 10 µg/mL 	IC50 = 8.31 µg/mL; inhibited XO activity (Dira, Eka, Fitrianda, 2014)

CONCLUSION

Based on the analysis of several natural ingredients with potential antihyperuricemia activity, it can be concluded that turmeric rhizomes (*Curcuma domestica* Val), kepel leaves (*Stelechocarpus burahol*), mangosteen peel (*Garcinia mangostana* L.), and pure honey have promising effects in lowering uric acid levels. Turmeric has potent anti-inflammatory and XO-inhibitory activities because of its curcuminoid, gingerol, and shogaol concentrations. Kepel leaves, although less active when used alone, exhibit flavonoid-based XO inhibition and become more effective when combined with conventional medications such as allopurinol. Mangosteen peel, which contains xanthonenes, flavonoids, and tannins, has been shown to inhibit XO activity and reduce uric acid levels in vivo. Pure honey contributes synergistically by increasing antioxidant activity and aiding uric acid removal, with no known negative effects.

Overall, the reviewed literature suggests that these natural substances, alone or in combination, have significant promise as alternative or complementary treatments for hyperuricemia. Their safety profiles, natural availability, and bioactive chemicals provide a solid platform for future studies and clinical applications in treating high uric acid levels and preventing consequences such as gout.

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