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Therapeutic Synergy of Combination of *Kaempferia galanga* and *Zingiber officinale* Extracts on Hyperuricemia-Induced Arterial Stiffness

Patonah Hasimun*, Yoga A. R. Muzaki, Jajang J. Sodik, Ika K. Sukmawati, R. Herni Kusriani
Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Bhakti Kencana University, Bandung, West Java, Indonesia

Abstract
Hyperuricemia, characterized by high uric acid levels, is associated with an elevated risk of cardiovascular diseases. Xanthine oxidoreductase (XOR), an enzyme central to uric acid generation, is implicated in oxidative stress and diminished vascular function. It has become a focal point for potential therapeutic interventions. This investigation aimed to assess the influence of combined ethanol extracts on xanthine oxidase activity and arterial rigidity in hyperuricemic rat models. Furthermore, the research sought to explore these extracts' potential in managing hyperuricemia and its associated vascular disorders. Hyperuricemia was established in Wistar rats by administering potassium oxonate at 4.5 mg/kg via injection. A total of 25 rats were divided into five groups: a normal control group receiving 0.5% CMC, a positive control group with hyperuricemia, a reference group treated with allopurinol (1.8 mg/kgBW), and two experimental groups receiving extracts from *Kaempferia galanga* L. and *Zingiber officinale* (KGZE) at doses of 50 mg/kgBW and 100 mg/kgBW. All rats consumed 25% fructose in their drinking water for 28 days. This study measured uric acid levels and arterial stiffness, revealing that KGZE significantly reduced uric acid levels and improved arterial stiffness, indicating its potential as an XOR inhibitor.

Keywords: Arterial stiffness, hyperuricemia, *Kaempferia galanga* L., xanthine oxidase, *Zingiber officinale*

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*Corresponding author:
patonah@bku.ac.id

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Terapi Sinergi Kombinasi Ekstrak *Kaempferia galanga* dan *Zingiber officinale* terhadap Kekakuan Arteri yang Diinduksi Hiperurisemia

Abstrak
Hiperurisemia, yang ditandai dengan peningkatan kadar asam urat dalam darah, dikaitkan dengan peningkatan risiko penyakit kardiovaskular. Enzim xantin oksidoreduktase (XOR) terutama mengatur produksi asam urat, yang berkontribusi terhadap stres oksidatif dan gangguan fungsi vaskular. Dengan demikian, XOR adalah target yang menjanjikan untuk intervensi terapeutik. Penelitian ini bertujuan untuk mengevaluasi efek ekstrak etanol gabungan pada *Kaempferia galanga* L. dan *Zingiber officinale* (KGZE) terhadap aktivitas xantin oksidase dan kekakuan arteri pada tikus hiperurisemia dan mengeksplorasi potensinya untuk mengobati hiperurisemia dan komplikasi vaskular terkait. Hiperurisemia diinduksi pada tikus Wistar jantan dengan menyuntikkan injeksi kalium oksonat 4,5 mg/kg. Sebanyak 25 ekor tikus dibagi menjadi lima kelompok: kelompok kontrol normal yang menerima CMC 0,5%, kelompok kontrol positif dengan hiperurisemia, kelompok referensi yang diobati dengan allopurinol (1,8 mg/kgBB), dan dua kelompok eksperimental yang menerima KGZE dengan dosis 50 mg/kgBB dan 100 mg/kgBB. Perawatan diberikan melalui *gavage oral*, dan semua tikus mengkonsumsi 25% fruktosa dalam air minum mereka selama 28 hari. Penelitian ini menunjukkan bahwa KGZE secara signifikan mengurangi kadar asam urat dan meningkatkan kekakuan arteri, yang menunjukkan potensinya sebagai penghambat XOR.

Kata Kunci: Hiperurisemia, *Kaempferia galanga* L., kekakuan arteri, xantin oksidase, *Zingiber officinale*

1. Introduction

Elevated blood uric acid levels characterize a medical condition known as hyperuricemia. Uric acid, which results from the breakdown of purines, has no known physiological functions. Three primary origins contribute to uric acid generation: the ingestion of purines through dietary sources, converting nucleic acids found in tissues to purine nucleotides, and the de novo production of purine bases within the body.[1,2] The Indonesian Ministry of Health (2022) defines hyperuricemia as a condition in which blood uric acid levels rise above 6.8 mg/dL in men and 6.0 mg/dL in women.[3] Elevated uric acid levels are commonly observed in people with metabolic syndrome, a condition associated with an elevated risk of several health complications. These include high blood pressure, diabetes, kidney diseases, heart-related problems, and liver disorders.[4]

The International Diabetes Federation (IDF) reported in 2018 that metabolic syndrome affected approximately 20-25% of the world's population.[5] The incidence of metabolic syndrome in Indonesia reached 21.8% in 2018.[6] The Global Health Data Exchange (GHDx) and the World Health Organization (WHO) reported that in 2017, an estimated 7.44 million people worldwide faced an elevated risk of metabolic syndrome due to hyperuricemia, a condition marked by excessive uric acid concentrations in the blood.[7,8] Elevated blood uric acid levels, known as hyperuricemia, are a significant risk factor for the development of metabolic syndrome. This connection stems from the ability of UA to induce insulin resistance, promote inflammation, and generate oxidative stress, which are all fundamental aspects of metabolic syndrome.[9] The condition is more common among males, with a 10% occurrence rate, compared to females, who experience it at a lower rate of 6%.[10] In Indonesia, gout affects 11.9% of the population, with the highest occurrence rate among those aged 75 years and above, reaching 54.8%.[6]

The xanthine oxidoreductase (XOR) facilitates the oxidative hydroxylation process, transforming hypoxanthine into xanthine. Subsequently, xanthine is converted into uric acid, a reaction that generates reactive oxygen species (ROS). In serum, uric acid typically exists as ions and salts, referred to as urate and uric acid. Clinically, hyperuricemia is defined as an abnormally high uric acid level in blood. This condition can arise from two primary mechanisms: the overproduction of uric acid or inadequate elimination of this compound from the body. This condition has been well established as a primary contributing factor in the development of gout.[11]

Elevated uric acid levels reduce nitric oxide (NO) production in endothelial cells or diminish its effectiveness through chemical reactions. Activation of the renin-angiotensin system triggered by high uric acid concentrations can also hinder endothelial NO production. The resulting decrease in NO availability leads to endothelial dysfunction and enhanced vascular tone, potentially contributing to arterial rigidity. Additionally, the renin-angiotensin-aldosterone system plays a role in increasing the stiffness of the endothelial cell cytoskeleton and promoting extracellular matrix fibrosis. Oxidative stress may facilitate the activation of TGF-ß1 by angiotensin 2, which stimulates vascular fibrosis. TGF-ß1 promotes the synthesis of proteoglycans, fibronectin, and collagen, thereby increasing vascular wall stiffness. Furthermore, uric acid-induced oxidative stress may promote the production endothelin-1, a potent vasoconstrictor that enhances arterial stiffness.[12]

Medications that reduce uric acid levels, such as the XOR inhibitor, allopurinol, are commonly prescribed for gout treatment.[11] Nevertheless, allopurinol causes adverse reactions that result in patients not adhering to treatment, including cutaneous eruptions, decreased white blood cell counts, digestive system issues, and hives.[1]

Medicinal plants can be found in various forms, including intentionally cultivated, naturally occurring in the wild, or processed into pharmaceutical products. These plants offer diverse applications, including ingestion, external use, cleansing, immersion, and respiratory intake. The effectiveness of medicinal plants stems from their interaction with cellular receptors, which enable them to deliver essential chemical components or triggers for therapeutic effects.[13,14]

Many herbal treatments combine plant species in a single preparation or blend various botanical products. This complexity in medicinal mixtures creates significant potential for interactions between the active ingredients.[15] When multiple active components are combined, they can produce synergistic or antagonistic outcomes.[16] A key principle in pharmaceutical research related to traditional medicine is that multiple ingredients in a single preparation can work together to produce enhanced effects. This can occur by targeting various sites or improving the active compounds' dissolution. Recent studies have demonstrated that combining herbs can lead to synergistic effects through multiple mechanisms. These include acting on several targets simultaneously, minimizing adverse reactions, and enhancing the absorption of crude herbal extracts.[16]

Researchers have identified two plants from the Zingiberaceae family that are thought to exhibit antihyperuricemic effects: aromatic ginger rhizomes

(*Kaempferia galanga*) and ginger (*Zingiber officinale*). Studies have suggested that species within the Zingiberaceae group can suppress xanthine oxidase activity.[17] Yumita et al. (2013) demonstrated that extracts from aromatic ginger rhizomes inhibited xanthine oxidase activity.[18]

Ginger is rich in bioactive substances including 6-gingerol, shogaol, paradol, and several phenolic acids. These compounds contribute to the anti-inflammatory, antioxidant, and anti-apoptotic properties.[19] The methanol extract from ginger (*Zingiber officinale*) rhizomes demonstrated potent inhibitory effects on xanthine oxidase.[20]

Recent studies have demonstrated that aromatic ginger and ginger rhizomes can reduce uric acid levels and suppress xanthine oxidase activity. Nevertheless, there is a lack of research examining their antihyperuricemic effects in animal models of hyperuricemia. This study aimed to fill this knowledge gap by investigating the antihyperuricemic properties of a combination of aromatic ginger (*Kaempferia galanga*) and ginger (*Zingiber officinale*) extracts on hyperuricemia-induced arterial stiffness. This study seeks to broaden our knowledge of the potential therapeutic uses of these compounds in treating conditions associated with hyperuricemia.

2. Materials and Methods

2.1. Ethical Considerations for Animal Research

Animal research ethics clearance was obtained under certificate 115/UN6. KEP/EC/2024. Ethical testing was mandatory for all experimental protocols involving animals. The research received medical ethics approval from Padjadjaran University, Sumedang, Indonesia.

2.2. Plant Materials Authentication

The rhizomes of *Kaempferia galanga* L. and *Zingiber officinale* were obtained from the Spice and Medicinal Plant Instrument Standard Testing Center in Bogor, West Java. Plant specimens were authenticated at Padjadjaran University's Plant Taxonomy Laboratory, West Java, Indonesia. Authentication certificates were granted numbers 31/HB/02/2024 for *K. galanga* and 30/HB/02/2024 for *Zingiber officinale*. Phytochemical analysis was performed to identify the presence of various secondary metabolites including alkaloids, flavonoids, saponins, tannins, and steroid triterpenoids.

2.3. Extract Preparation

The preparation of *Kaempferia galanga* and *Zingiber officinale* rhizomes involved several steps. Initially, rhizomes were washed, sliced, and dried at 37°C. The dried material was then pulverized and immersed in 70% ethanol for three days in a dark environment. After this period, the mixture was filtered, and the resulting liquid extract was concentrated using a rotary evaporator at 40°C.

2.4. Experimental Animal Handling

The study used male Wistar rats, aged 2-3 months and weighing 200–250 g. These animals were kept in a laboratory environment with controlled conditions: temperature ranging from 24 to 26°C, humidity between 70 and 75%, and a light-dark cycle of 12 h each. A 10-day acclimatization period was used for the test subjects. The rats were provided standard feed and had unrestricted access to water. To induce hyperuricemia, the animals were given drinking water containing 25% fructose over 28 days, followed by intramuscular injection of potassium oxonate (4.5 mg/kg BW) on the final day. The rats were then categorized into five groups: normal control, positive control, allopurinol (1.8 mg/kg), and two groups receiving a combination *Kaempferia galanga* and *Zingiber officinale* ethanolic extract (KGZE). All groups except the normal control group underwent hyperuricemia induction.

2.5. Quantification of Xanthine Oxidase (XO) Inhibitory Capacity

The assessment of xanthine oxidase (XO) inhibitory activity was assessed using a 96-well microplate reader. A blank was prepared with 115 µL of phosphate buffer (pH 7.5), whereas the control mixture contained 85 µL of buffer and 30 µL of xanthine oxidase. The experimental samples were formulated by combining 50 µL of allopurinol or KGZE, 35-65 µL of buffer, and 30 µL of XO (0.2 U/mL). The samples were then incubated for 15 minutes at 25°C. Subsequently, xanthine substrate at a concentration of 60 µg/mL was introduced into the mixture, which was then incubated for an additional 30-minute incubation period. The reaction was terminated by introducing 25 µg/mL of 1M HCl. Absorbance measurements were recorded at 290 nm, and all activity assessments were performed in triplicate. The extent of inhibition was quantified using the following formula:

$$Percentage\ of\ inhibition: \frac{(A-B)}{A} \times 100\%$$

In this equation, A represents the difference between the absorbance values of the control and blank control, whereas B denotes the difference between the sample and blank absorbance readings.

2.6. Arterial Stiffness Evaluation

The assessment of arterial stiffness was conducted on days 0, 14, and 28 utilizing the pulse wave velocity (PWV) technique described by Zakaria & Hasimun (2017). This approach employs an electrocardiogram sensor to capture the electrical activity of the heart through electrodes placed on the right palm, left palm, and right foot. Simultaneously, a photoplethysmography sensor positioned at the base of the tail was used to monitor changes in blood flow. Higher PWV measurements are indicative of increased arterial stiffness.21 The experiment was carried out at the Pharmacology Laboratory of Bhakti Kencana University at Faculty of Pharmacy.

2.7. Measurement of Uric Acid Concentration

Blood was obtained from the orbital sinus and centrifuged for 5 min at 3000 rpm to isolate plasma. The reaction mixture, consisting of 5 µL plasma and 500 µL uric acid reagent, was incubated at an ambient temperature (20-25°C) for 10 min. The uric acid content was quantified using a Microlab 300 instrument at a wavelength of 546 nm.

2.8. Xanthine Oxidase (XO) Inhibition Analysis Using Rat Hepatic Tissue

The study examined xanthine oxidase (XO) inhibition using 20% liver homogenate from all experimental groups. The homogenate was combined with the xanthine substrate at concentrations of 0.2, 0.4, 0.6, and 0.8 ppm. Measurements were performed using liver homogenates from healthy rats. XO inhibition was evaluated through spectrophotometric analysis at 576 nm, utilizing 0.2 U/mL of XO enzyme. The protocol included a 15-minute pre-incubation for solution preparation and a 30-minute enzymatic reaction. Measurements were taken for the blank control solutions, controls, blank samples, and test samples. The control assessed XO activity without extracts, whereas the blank control confirmed the absence of interference with enzyme activity.

2.9. Molecular Docking Validation of Xanthine Oxidoreductase

AutoDock version 4.2.3 was utilized to conduct molecular docking validation. The protein underwent preliminary preparation, and Discovery Studio was used to extract the native ligand from the protein before re-docking it into the target protein. The grid center was established near the center of the ligand, encompassing all binding site residues. The grid box was determined by setting the native ligand's central region and executing docking with 100 Genetic Algorithm (GA) runs, a medium number of evaluations, and the Lamarckian Genetic Algorithm (LGA). Validation was considered successful when the Root Mean Square Deviation (RMSD) remained below 2 Å.[22]

2.10. Molecular Docking Simulation

Docking simulation of the test ligand to the target protein was performed using AutoDock version 4.2.3. Based on the validation process results, adjustments were made to the grid box size and position. The docking results were evaluated by examining the binding free energy (Δ G) and inhibition constant (KI). The binding interactions between the test ligand and the target protein were analyzed using two software applications: Discovery Studio Visualizer 2016 and Visual Molecular Dynamics. These tools enabled visualization of docking results, highlighting the intermolecular bonds formed between the ligand and specific amino acid residues within the protein structure.[22]

2.11. Data Analysis

The findings were expressed as mean values accompanied by standard deviation (SD), derived from five specimens per experimental group. The data were subjected to statistical analysis using one-way ANOVA, conducted with SPSS 25.0. Results were considered statistically significant when the p-value was below 0.05 ($p<0.05$).

3. Results

The initial stage of this study encompassed a phytochemical examination of extracts obtained from *Kaempferia galanga* and *Zingiber officinale* following maceration to ascertain their constituent elements. Biochemical compounds were qualitatively assessed by subjecting the extracts to specific reagents. The results indicated that *K. galanga* extract contained alkaloids, flavonoids, tannins, and triterpenoids. These observations are consistent with prior investigations that identified these compounds as bioactive constituents in *Kaempferia galanga* during phytochemical screenings.[23]

Zingiber officinale extract contained alkaloids, tannins, flavonoids, and triterpenoids. This finding aligns with earlier research that identified these compounds during phytochemical analysis.[24] Additionally, previous research has indicated that the antihyperuricemic properties of *Zingiber officinale* extract can be attributed to its flavonoid content, which serves as the active component.

The IC_{50} value range for KGZE reached a concentration

Table 1. KGZE IC_{50} Calculation as an Inhibitor of Xanthine Oxidase

Replication	a	b	y	IC_{50} (g/mL)	Average ± SD
1	16.77	10.55	50	23.32	
2	17.65	10.29	50	23.23	23.22±0.11
3	17.77	10.27	50	23.10	

of about 23.22 µg/mL, while the standard drug allopurinol exhibited an IC_{50} value of approximately 1.54 µg/mL (Table 1). A lower IC50 value indicates a more potent inhibitory activity, demonstrating that a lower concentration can produce a significant inhibitory effect. The observed XO inhibition in the liver samples was illustrated in Figure 1.

Figure 1 illustrated that the control group, displaying 39.27% XO inhibition without inhibitors, was statistically distinct from all other groups ($p<0.05$), revealing inherent XO suppression in the hepatic tissue. The group administered allopurinol, a competitive inhibitor, exhibited a markedly elevated inhibition rate of 82.63% ($p<0.05$). Allopurinol attaches to XO, converting it to oxypurinol through oxidation, impeding enzyme activity.

Uric acid measurements were performed before and after fructose and potassium oxonate administration on day 28. Blood was drawn from the orbital sinus vein, selected for its simplicity and reduced the likelihood of blood cell rupture. This technique is frequently employed in studies that utilize pre-test and post-test designs. The average uric acid concentrations in the rats, determined using a Microlab 300 with a wavelength of 546 nm, are shown in Figure 2.

Figure 2 demonstrates that the initial uric acid levels were similar across all groups at T0 ($p>0.05$), indicating a uniform starting point. However, by T28, after the induction process, significant differences were observed ($p<0.05$) when compared with the normal control group, confirming the successful increase in uric acid concentrations. Administration of allopurinol (1.8 mg/kg BW) resulted in a substantial decrease in uric acid concentrations compared with the positive control ($p<0.05$), verifying its effectiveness. Additionally, KGZE 50 exhibited a considerable reduction in uric acid levels relative to the positive control group ($p<0.05$), highlighting its potential as a uric acid-reducing compound. In contrast, KGZE 100 showed no significant difference from the positive control, suggesting that higher doses of KGZE may be ineffective in reducing uric acid levels and could lead to increased uric acid concentrations.

Figure 3 illustrates that allopurinol showed no significant difference from the control group on day 28, suggesting its effectiveness in inhibiting arterial stiffness. Moreover, KGZE 50 exhibited superior efficacy in decreasing pulse wave velocity (PWV) compared to KGZE 100 mg/kg BW. By day 28, the PWV measurement for the KGZE 100 group differed significantly from that of the normal group, whereas KGZE 50 displayed no significant variance from the normal group.
Using DSV and VMD software, visualization was performed to examine the interactions between the ligands and their target proteins by evaluating conformational fit (Figure 4). The conformational suitability of the test ligands was compared with that of the native ligand (green) to confirm the binding free energy values, because active ligands must bind to specific amino acid residues at the binding site to inhibit or induce activity.

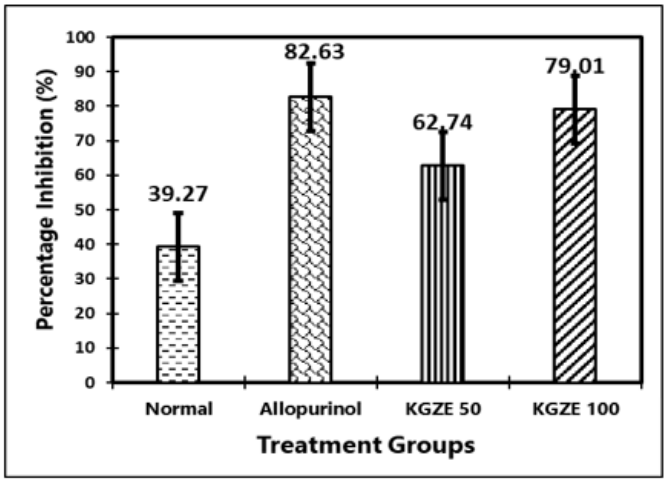

Figure 1. Inhibition of Xanthine Oxidase (XO) Enzyme in Hepatic Tissue

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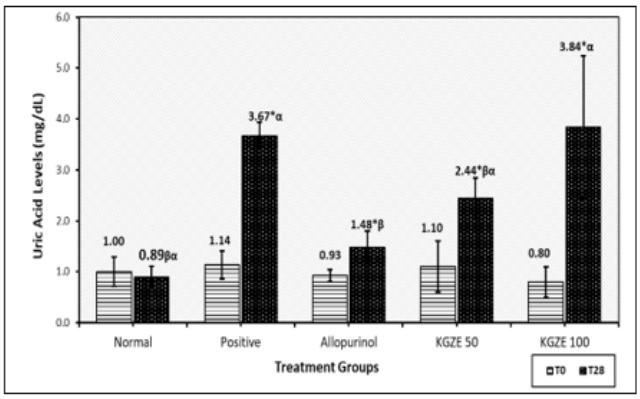

Figure 2. Uric Acid Measurements. KGZE: Ethanolic extract combination of *Kaempferia galanga* and *Zingiber officinale* at 50 mg/kg BW, 100 mg/kg BW; (*) Sta tistically significant variance from the normal group (p<0.05); (β) statistically substantial devia tion from the positive group (p<0.05); (α) statisti cally significant disparity from the allopurinol group (p<0.05).

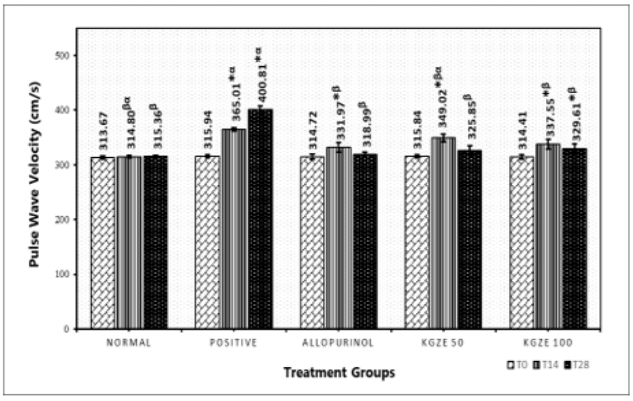

Figure 3. PWV Measurement. KGZE: Combination of *Kaempferia galanga* and *Zingiber officinale* ethanolic extract 50 mg/kg BW, 100 mg/kg BW; (*) Statistically significantly different from the normal group (p<0.05); (β) Statistically significantly different from the positive group (p<0.05); (α) Statistically significantly different from the allopurinol group (p<0.05).

4. Discussion

The enzyme xanthine oxidase (XO) facilitates the conversion of hypoxanthine to uric acid, while concurrently generating reactive oxygen species. Abnormal XO activity can result in elevated uric acid levels (hyperuricemia), potentially causing gout and oxidative tissue damage.[25] The three replicates in the linear regression analysis demonstrated consistent measurements, indicating that KGZE successfully inhibited XO. Increased concentrations of KGZE appear to enhance antioxidant activity and reduce inflammation more efficiently. The flavonoids found in KGZE potentially play a role in suppressing proinflammatory cytokines and improving the efficiency of antioxidant enzymes such as superoxide dismutase and catalase.[26]

A dose-related mechanism could explain this effect, wherein excessive active compounds such as flavonoids or polyphenols might trigger unexpected outcomes. These could include heightened generation of reactive oxygen species (ROS) or an overburden of metabolic pathways that regulate uric acid, potentially worsening inflammation and oxidative stress instead of reducing them. Furthermore, higher doses could overwhelm the body's antioxidant defense systems, possibly leading to compromised uric acid elimination or modified enzyme function in purine metabolism of purines.[27]

The enzyme uricase is inhibited by potassium oxonate, resulting in hyperuricemia owing to the blocked conversion of uric acid to allantoin.[28] High uric acid levels in the blood contribute to arterial hardening by triggering inflammatory responses and oxidative stress. This process leads to increased production of collagen and reduced elasticity of the blood vessels.[29] Uric acid triggers the activation of the NLRP3 inflammasome, resulting in the secretion of inflammatory cytokines IL-1β and IL-1830. Conversely, KGZE, which contains high levels of flavonoids, exerts an anti-inflammatory effect by inhibiting the NF-κB pathway and reducing the production of cytokines, such as TNF-α and IL-6.[30,31]

Allopurinol effectively combats oxidative stress and inflammatory responses in the body by lowering uric acid concentration and diminishing the presence of free radicals.[32] Current research indicates that allopurinol enhances endothelial function and decreases arterial rigidity, as the reduced PWV measurements demonstrate. These findings suggested that allopurinol successfully reduced arterial rigidity induced by elevated uric acid levels in the blood.[33] Research findings support these results, showing that healthy arteries are associated with consistently low pulse wave velocity (PWV) measurements.[34]

The measurement of pulse wave velocity (PWV) relies on the fundamental concept of utilizing electrocardiogram (ECG) and photoplethysmography (PPG) sensors. An electrocardiogram (ECG) records the heart's electrical activity by using electrodes placed on the right and left hands, as well as the right and left feet. A PPG sensor was attached to the base of the tail to measure fluctuations in the blood volume. The PPG signal is a secondary reference point, indicating the instant when the blood is ejected from the heart.[21]

The PWV method is a convenient and noninvasive technique for accurately assessing arterial stiffness in

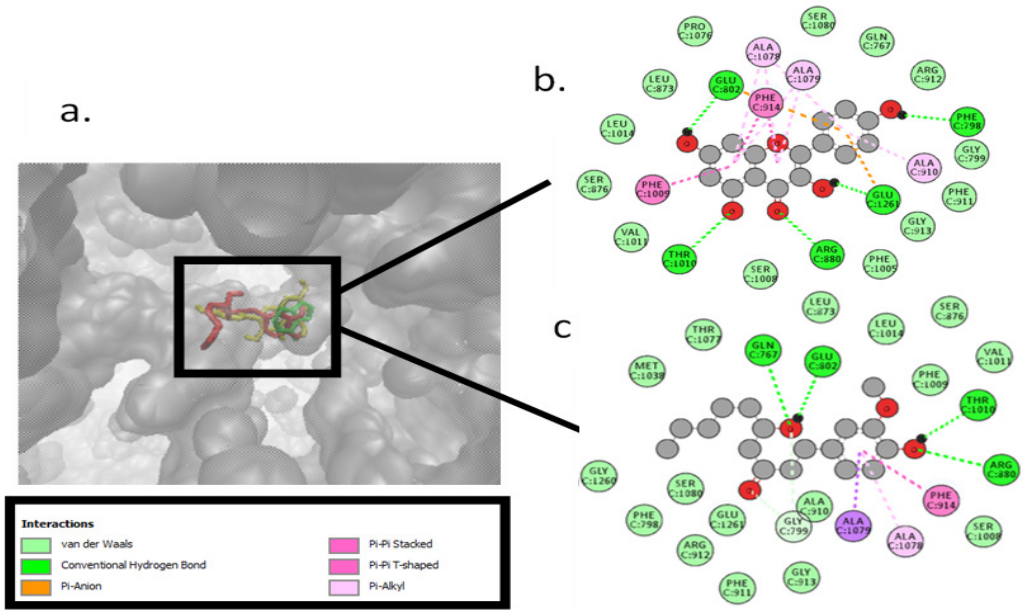

Figure 4. Visualization of molecular docking of ligand-protein XOR, Kaempferol, Gingerol. Green: Native Ligand, Yellow: Kaempferol, and Red: Gingerol. Visualization of the molecular docking of ligand-protein (a) XOR, (b) kaempferol, and (c) gingerol.

experimental animals without requiring surgery. The PWV values obtained indicate how hard the heart works, and can serve as a reference for diagnosing arterial stiffness. High PWV values indicate increased arterial stiffness, reducing arterial wall flexibility. This inflexibility is due to the inability of the vessel walls to store energy from each blood pressure pulse, resulting in a loss of elasticity.[35]

This study investigated how KGZE affected uric acid reduction in rats with hyperuricemia, primarily by assessing arterial stiffness through pulse wave velocity (PWV). PWV indicates arterial elasticity, with elevated readings suggesting decreased flexibility and a heightened cardiovascular risk.

The interaction results of the test ligands (kaempferol and gingerol) with xanthine oxidoreductase demonstrated binding to key amino acid residues, Arg880 and Glu802.[36,37] These interactions involve hydrogen bonds between hydrogen atoms and F, O, or N atoms. Hydrogen bonds are stronger and more specific than hydrophobic interactions because they influence the physicochemical properties of a compound, such as its boiling point, solubility, melting point, and acidity, all of which can affect its biological activity of the compound.[38]

Interaction with key amino acid residues, such as Arg880 and Glu802, suggested that the ligands have an affinity and inhibitory effect by interacting with critical residues. Additionally, hydrophobic interactions play a crucial role in merging the ligand molecule's non-polar regions with the target's non-polar regions. The formation of hydrophobic bonds helps minimize the interactions between non-polar residues and water.[39] These interactions are essential for the stabilization and function of the ligand-target complex, influencing its binding strength and biological activity.

5. Conclusion

Research on hyperuricemic animal models has revealed that combining extracts from aromatic ginger (*Kaempferia galanga* L.) and ginger (*Zingiber officinale*) potently inhibits xanthine oxidase. The extract blend showed optimal efficacy at 100 mg/kg BW, while a lower dose of 50 mg/kg BW still offers significant therapeutic advantages, including reduced uric acid levels and improved arterial elasticity. These results indicate that this extract combination could be a valuable therapeutic option for addressing hyperuricemia and mitigating cardiovascular risks, potentially leading to future clinical applications.

Conflict of Interest

The authors declare there are no conflicts of interest related to this work.

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