

## Pharmacological Evaluation Of *Sechium edule* Extract On Hyperuricemia: Biochemical Analysis In Rats Induced By Potassium Oxonate

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### Abstract

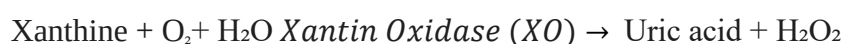
Hyperuricemia, a condition characterized by high blood uric acid levels, is a trigger for gout and kidney disorders. Conventional treatments such as allopurinol carry the risk of serious side effects. This study evaluated the potential of *Sechium edule* ethanol extract (ESEE) as an in vivo experimental treatment. The study used male rats induced with potassium oxonate to induce hyperuricemia. The test animals were divided into normal, negative, positive (allopurinol), and two groups receiving doses of ESEE 200 and 400 mg/kgBW. The results showed that administration of ethanol extract of bay leaves (ESEE) at a dose of 400 mg/kgBW significantly ( $p < 0.05$ ) reduced serum uric acid levels compared to the control group. Its effectiveness is equivalent to allopurinol. Biochemical analysis showed that in vivo administration of ESEE was able to inhibit *xanthine oxidase* enzyme activity in the liver of mice by up to 47.3%. Flavonoids such as apigenin are believed to be responsible for this inhibitory mechanism. It can be concluded that *Sechium edule* ethanol extract has antihyperuricemic activity comparable to allopurinol in reducing serum uric acid levels and inhibiting *xanthine oxidase* enzyme activity. This extract works through a dual mechanism by suppressing uric acid production and protecting the kidneys from damage. These findings open up opportunities for the development of *Sechium edule* as a safe and efficient herbal medicine for the management of gout.

**Keywords:** *Sechium edule*, Hyperuricemia, Xanthine Oxidase, Potassium Oxonate, Uric Acid

### 1. INTRODUCTION

Hyperuricemia has become a significant global health problem, not only as a major risk factor for *gouty arthritis* (gout) but also as an independent prognostic indicator for various cardiometabolic diseases, including hypertension, type 2 diabetes mellitus, and chronic kidney disease (CKD) (Pitaloka Putri et al., 2021). Physiologically, hyperuricemia is defined as a condition where serum uric acid levels exceed 6.8 mg/dL. When this threshold is exceeded, urate crystallization occurs in the synovial tissue, triggering an acute inflammatory response mediated by the NLRP3 inflammasome, causing severe pain and permanent joint damage if left

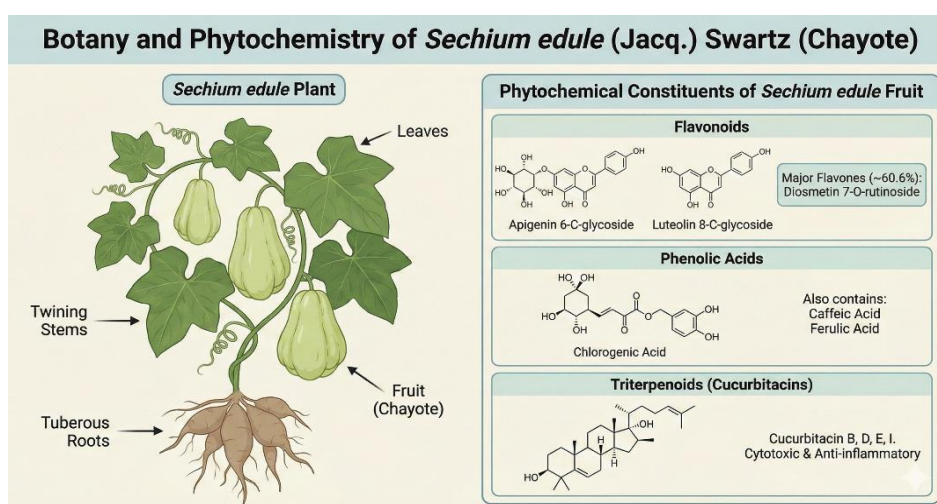
untreated (Xu et al., 2021). Humans lack the enzyme uricase, which breaks down uric acid. As a result, our uric acid levels are naturally higher and we are prone to hyperuricemia (Zhou et al., 2024). This is where the role of the enzyme *xanthine oxidoreductase* (XOR) becomes crucial. This enzyme converts hypoxanthine to xanthine, then xanthine to uric acid, the last two steps of purine metabolism. XOR has two forms that can be converted: xanthine dehydrogenase (XDH) and xanthine oxidase (XO) (Xu et al., 2021). Under normal conditions, XDH is dominant and works with NAD<sup>+</sup>. However, during oxidative stress or inflammation, XDH converts to XO. It is this form that is problematic: it produces free radicals such as superoxide anion and hydrogen peroxide as byproducts (Pauff & Hille, 2009). Thus, the same enzyme not only produces uric acid but also triggers oxidative stress, which damages blood vessels and kidneys.



Therefore, *xanthine oxidase* hyperactivity not only causes uric acid accumulation (hyperuricemia) but also triggers systemic oxidative stress that contributes to endothelial dysfunction and kidney damage. This makes *xanthine oxidase* inhibition a highly strategic dual therapeutic target (Xu et al., 2021). Allopurinol is the first-line treatment for hyperuricemia. It works by competitively inhibiting the xanthine oxidase enzyme at its active site, converting to oxypurinol, and then binding tightly to it, thereby halting uric acid production (Qurie et al., 2023). However, this effectiveness comes with risks. In patients with kidney disorders or carriers of the HLA-B\*58:01 allele, allopurinol can trigger fatal hypersensitivity reactions such as Stevens-Johnson syndrome (Gonçalo et al., 2013; Stamp et al., 2018; FitzGerald et al., 2020). Gastrointestinal disorders and liver damage are also commonly reported. Meanwhile, febuxostat has side effects on the heart. Probenecid and benzbromarone, which excrete uric acid through the kidneys, are dangerous for people with kidney stones or kidney disorders (Xu et al., 2021). These limitations have prompted the need for safer natural alternatives without compromising effectiveness. Chayote has long been known as an ordinary vegetable, but behind that, it holds a legacy of traditional medicine. Decoctions of its leaves and fruit have been used for generations to treat hypertension, atherosclerosis, and facilitate urination (Lombardo-Earl et al., 2014). These properties are apparently not just myths. Modern research has found that bitter melon is rich in flavonoids such as apigenin and luteolin, compounds that are structurally similar to xanthine, a natural substrate of the enzyme xanthine oxidase. This similarity allows

flavonoids to inhibit the enzyme's activity, thereby reducing uric acid production (Pauff & Hille, 2009; Pitaloka Putri et al., 2021). Interestingly, most research has focused on the leaves, even though the fruit is the most commonly consumed and easily available part. In fact, chayote fruit has been proven to have a diuretic effect that helps eliminate uric acid (Marie Nancy Volamiadana RABIA et al., 2025) and antioxidant activity that protects the body from oxidative stress (Vieira et al., 2022), two mechanisms that are highly relevant in the management of hyperuricemia. This study aims to address this gap by specifically testing the efficacy of ethanol extract from Siamese pumpkin fruit using ethanol as a solvent to optimally extract flavonoid compounds (Díaz-de-Cerio et al., 2019) in experimental animals with hyperuricemia. To test the antihyperuricemic efficacy *in vivo*, the use of a valid animal model is crucial. Mice and rats naturally possess active uricase enzymes, which maintain their uric acid levels very low (0.5-2.0 mg/dL) compared to humans. To mimic human hyperuricemia conditions, this uricase activity must be inhibited. Potassium oxonate (PO) is a selective competitive uricase inhibitor. Intraperitoneal injection of PO causes a rapid and significant increase in plasma uric acid levels, creating a temporary or chronic hyperuricemia model depending on the duration of administration (Xu et al., 2021). This model is considered the gold standard in anti-gout drug screening because it allows direct evaluation of agents that work through urate production inhibition (such as XOIs) or increased urate excretion.

*Sechium edule* (Jacq.) Swartz is a perennial vine from the *Cucurbitaceae* family. This plant has roots, vines, and fleshy fruits that vary in shape and color, but are generally pale green with a wrinkled surface (Madrigal-Santillán et al., 2024).

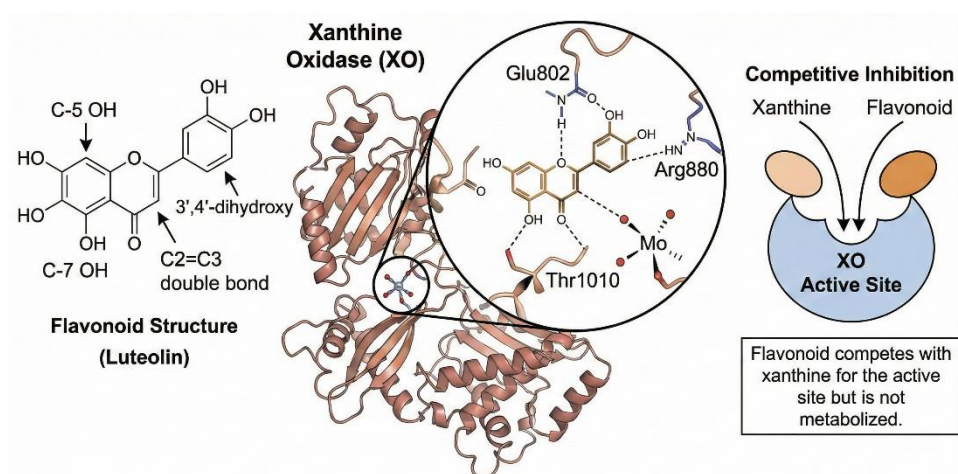


**Figure 1.** Botanical and phytochemical overview of *Sechium edule*.

Note: The image was generated using Google Gemini 1.5 Pro from the prompt "[Generate a high-quality scientific infographic on a clean, light-colored background titled 'Botany and Phytochemistry of *Sechium edule* (Jacq.) Swartz (*Sechium edule*)'. The left side should display a botanical illustration of the *Sechium edule* plant, showing the twining stem, heart-shaped green leaves, hanging pear-shaped fruit, and tuberous roots, with clear anatomical labels. The right side should be divided into three structured panels for 'Phytochemical Components of *Sechium*

edule Fruit': (1) 'Flavonoids' displaying the 2D chemical structures of Apigenin 6-C-glycoside and Luteolin 8-C-glycoside; (2) 'Phenolic Acids' displaying the 2D structure of Chlorogenic Acid and listing Caffeic Acid and Ferulic Acid; (3) 'Triterpenoids (Cucurbitacin)' displaying the complex steroid structure of Cucurbitacin and noting its cytotoxic and anti-inflammatory properties. Use professional and academic aesthetics with balanced composition and easy-to-read Times New Roman font.], by Google, 2024 (<https://gemini.google.com/>).

Chayote fruit is rich in flavonoids, particularly apigenin and luteolin along with their glycosides, which are responsible for antioxidant activity and inhibition of uric acid-causing enzymes (Pitaloka Putri et al., 2021). Studies indicate that approximately 60.6% of its compounds are flavones, with diosmetin 7-O-rutinoside as the primary component (Díaz-de-Cerio et al., 2019). Additionally, it contains phenolic acids (chlorogenic acid, caffeic acid, ferulic acid) that counteract free radicals (Vieira et al., 2019), as well as cucurbitacin triterpenoids (types B, D, E, I) that have strong anti-inflammatory properties (Varela et al., 2022) (Dai et al., 2023) (Delgado-Tiburcio et al., 2025). The interaction between flavonoids and *xanthine oxidase* has been studied in depth through enzyme kinetics and molecular modeling (*molecular docking*) studies. The basic structure of flavonoids (C6-C3-C6) has stereochemical similarities to the purine ring of the xanthine substrate.



**Figure 2.** Mechanism of flavonoid interaction with xanthine oxidase and molecular modeling of luteolin inhibition.

Note: Image generated using Google Gemini 1.5 Pro based on the author's descriptive prompt [Generate a high-resolution scientific infographic on a white background illustrating the interaction between Luteolin and the Xanthine Oxidase (XO) enzyme. The visual must include: (1) A detailed 2D chemical structure of Luteolin with specific annotations for C-5 OH, C-7 OH, the 3',4'-dihydroxy group, and the C2=C3 double bond. (2) A 3D ribbon diagram of the central structure of the Xanthine Oxidase protein. (3) An enlarged inset circle showing the molecular docking of Luteolin within the active site of XO, highlighting hydrogen bond interactions with residues Glu802, Thr1010, Arg880, and proximity to the Molybdenum (Mo) cofactor. (4) Conceptual diagram on the right depicting competitive inhibition between Xanthine and Flavonoids against the active site of XO. Use professional and academic aesthetics with balanced composition and easy-to-read Times New Roman font.], by Google, 2024 (<https://gemini.google.com/>).

The image shows the presence of hydroxyl groups at positions C-5 and C-7 on ring A, as well as a catechol pattern (3',4'-dihydroxy) on ring B (as in luteolin), which significantly increases the affinity of the bond with the enzyme (Pauff & Hille, 2009). Hydrogen bonds form

between the flavonoid hydroxyl groups and amino acid residues around the molybdenum center of the enzyme (Glu802, Arg880, and Thr1010). Double bonds on ring C maintain the planarity of the molecule, allowing effective intercalation into the narrow cleft of the enzyme's active site, thereby blocking access to endogenous substrates (Vieira et al., 2019). Inhibition kinetics are generally competitive or mixed, where flavonoids compete with xanthine to occupy the active site but are not metabolized by the enzyme, unlike allopurinol, which is a suicide substrate (Zheng et al., 2023; Wang et al., 2025). Indonesia is rich in antihyperuricemic plants. Bay leaves have been shown to lower uric acid through antioxidant effects and mild inhibition of xanthine oxidase (Pratama et al., 2024). Tempuyung, besides being known as a kidney stone dissolver, has anti-inflammatory effects on joints and the ability to inhibit xanthine oxidase with a strong category ( $IC_{50}$  23.37 ppm) (Parisa et al., 2021; Parisa et al., 2024). However, chayote offers different advantages. It is not just a medicine, but also a daily food ingredient with an exceptional safety profile. Toxicity tests show that doses of up to 5000 mg/kgBW do not cause toxic effects or liver and kidney dysfunction (Aguñiga-Sánchez et al., 2017). This combination of effectiveness and safety makes it an ideal candidate for long-term consumption, both as food and as a supplement.

## 2. METHODS

### 2.1. Design

This study was an *in vivo* laboratory experimental study with a completely randomized design (CRD) and a *pre-test and post-test control group design*. Ethical committee approval No. 049/E-KEPK/STIKES/BHM/V/2025. The study population consisted of male white mice (*Mus musculus*), selected for their stable response to chemical induction and genetic uniformity.

### 2.2 Tools and Materials

**Plant Materials:** Fresh *Sechium edule* fruit was obtained from Magetan Regency to minimize phytochemical variation due to environmental factors. Specimens were identified at B2P2TOOT Tawangmangu to ensure taxonomic accuracy.

**Chemical Materials:** 96% ethanol (Merck), Potassium Oxonate (Sigma Aldrich, No. Catalog 156124), Allopurinol (Sigma Aldrich), Uric Acid Reagent Kit (TBHBA enzymatic colorimetric method), *Xanthine Oxidase* Test Kit, CMC-Na (*sodium carboxymethyl cellulose*), distilled water, and standard rat feed.

**Equipment:** Metabolic cages, *rotary evaporator* (Buchi), UV-Vis spectrophotometer

(Shimadzu), cold centrifuge, micropipettes, oral probes, and syringes.

### 2.3 Preparation of *Sechium edule* Fruit Ethanol Extract (EESI)

The extraction method was selected based on an optimization study showing that ethanol is the best solvent for extracting flavonoids from the *Sechium edule* fruit matrix. According to research by Díaz-de-Cerio et al. (2019):

1. Preparation of Simplicia: Fresh fruit was washed thoroughly, sliced thinly, and dried in an oven at 40-50°C or dried in the air without direct exposure to sunlight to prevent thermal degradation of active compounds. The dried simplicia was then ground into fine particles (mesh size 40-60).
2. Maceration: Simplicia powder (1 kg) is soaked in 96% ethanol solvent at a ratio of 1:5 (weight/volume) for 3 x 24 hours at room temperature. Stirring is carried out periodically to maximize mass diffusion. 96% ethanol is chosen to maximize the extraction of aglycone flavonoids and less polar glycosides.
3. Evaporation: The macerate is filtered using Whatman No. 1 filter paper. The filtrate obtained is concentrated using a rotary vacuum evaporator at a temperature of 50°C with a rotation speed of 100 rpm until a thick extract (EESI) is obtained.
4. Standardization, the extraction yield was calculated, and qualitative phytochemical screening was performed to confirm the presence of flavonoids before use in *in vivo* tests.

### 2.4 Experimental Animals and Grouping

Thirty male rats (body weight 25-30 grams, age 2-3 months) were acclimated for 7 days in polycarbonate cages with a 12-hour light/dark cycle, temperature 25±2°C, and free access to standard feed and drinking water. The animals were randomly divided into 5 groups (n=6), Group I (Normal Control): Given standard feed + solvent (0.5% CMC-Na) orally + intraperitoneal saline injection. Group II (Negative Control): Induced with Potassium Oxonate + 0.5% CMC-Na orally. Group III (Positive Control): Induced with Potassium Oxonate + Allopurinol suspension at a dose of 10 mg/kgBW orally (Benchchem, 2025). Group IV (EESI 200): Induced with Potassium Oxonate + EESI extract at a dose of 200 mg/kgBW orally. Group V (EESI 400): Induced with Potassium Oxonate + EESI extract at a dose of 400 mg/kgBW orally.

#### Dose Determination:

The allopurinol dose of 10 mg/kgBW was selected based on human-to-rat dose conversion

and literature studies showing efficacy in mouse models. The extract doses of 200 and 400 mg/kgBW were determined based on preliminary studies showing that this dose range is effective for diuretic and antioxidant activity without toxicity.

## 2.5 Hyperuricemia Induction Protocol

Induction was performed using Potassium Oxonate (PO) at a dose of 250 mg/kgBW dissolved in physiological solution or an appropriate carrier (Pitaloka Putri et al., 2021). The injection was administered intraperitoneally (i.p.) one hour before administration of the test preparation (extract or allopurinol) every day for 14 days. This method ensures that uricase inhibition has occurred when the drug/extract reaches peak concentration in the plasma, allowing evaluation of the preventive and curative effects (Firdous Mumtaz et al., 2013).

## 2.6 Measurement of Parameters

1. Serum uric acid levels were measured using blood samples taken from the retro-orbital sinus or tail vein on day 0 (baseline), day 7, and day 14. The serum was separated by centrifugation at 3000 rpm for 15 minutes. Uric acid levels were measured using an enzymatic colorimetric method (*uricase peroxidase* reaction). The intensity of the *quinoneimine* color formed was measured at a wavelength of 520 nm (Pitaloka Putri et al., 2021).
2. Liver *Xanthine Oxidase* Activity: At the end of the study (day 15), the rats were humanely euthanized. The liver organs were isolated, washed with a cold phosphate buffer (pH 7.4), and homogenized. The supernatant from cold centrifugation (10,000 g, 20 minutes) was used as the enzyme source. XO activity was measured spectrophotometrically by monitoring the formation of uric acid from the xanthine substrate at a wavelength of 290 nm.

## 2.7 Data Analysis

Quantitative data are expressed as Mean  $\pm$  Standard Error of the Mean (SEM). Data normality was tested using the Shapiro-Wilk test. Statistical analysis was performed using *One-Way ANOVA* (Analysis of Variance) followed by *Tukey's HSD* test or *Duncan's Multiple Range Test* to test differences between groups. A p-value  $< 0.05$  was considered statistically significant.

### 3. RESULTS AND DISCUSSION

#### 3.1 Screening and Phytochemical Characterization of Extracts

The maceration extraction process of *Sechium edule* fruit produced a thick, greenish-brown extract with a yield of 15.73% (w/w). The results of qualitative phytochemical screening are presented in Table 1.

**Table 1.** Phytochemical Profile of *Sechium edule* Ethanol Extract (ESEE)

| Compound Group    | Detection Method        | Results                   | Molecular Potential Interpretation & Therapeutic                                                                                                                                                                                         |
|-------------------|-------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Flavonoids</b> | Mg + HCl + Amyl Alcohol | (+) Red                   | Contains a benzo- $\gamma$ -pyrone core structure. The main flavonoids in <i>S. edule</i> include apigenin and luteolin, which are known to be strong competitive inhibitors of the <i>xanthine oxidase</i> enzyme (Putri et al., 2021). |
| <b>Alkaloids</b>  | Dragendorff's reagent   | (+) Red Brick Precipitate | A class of basic nitrogen compounds. Potentially modulates renal transporters and suppresses pro-inflammatory cytokines (Li et al., 2024)                                                                                                |
| <b>Saponins</b>   | Foam Test (Shake)       | (+) Stable Foam           | Triterpenoid glycosides (including <b>Cucurbitacins</b> ). Demonstrates anti-inflammatory activity through inhibition of the NLRP3 inflammasome and diuretic effects (Lou et al., 2024)                                                  |
| <b>Tannins</b>    | FeCl <sub>3</sub>       | (+) Dark Black            | Polyphenolic compounds with high antioxidant capacity, functioning as superoxide radical scavengers produced during uric acid synthesis (Zagoskina et al., 2023)(Andrés et al., 2024)                                                    |

Specific parameter data indicate that the extract meets safety and stability standards, with a water content (7.65%) below the maximum limit of 10%, ensuring the extract's stability against enzymatic degradation and microbial growth during storage (Lee et al., 2023; Alqahtani et al., 2023; Alqahtani et al., 2023). The ash content (16.5%) is relatively high, reflecting the internal mineral richness (such as potassium) in *Sechium edule* fruit. The high potassium content synergizes with the diuretic effect, helping to alkalize urine and facilitate the excretion of uric acid. And Ethanol-Free, the negative ethanol test ensures the safety of the extract for *in vivo* applications without the risk of residual solvent toxicity (Hussain et al., 2025). In this study, the use of the maceration method with 96% ethanol solvent on 500 grams of *Sechium edule* fruit powder yielded 78.68 grams of concentrated extract. The yield value (15.73%) significantly exceeded the minimum threshold of 10% set by the Directorate General of

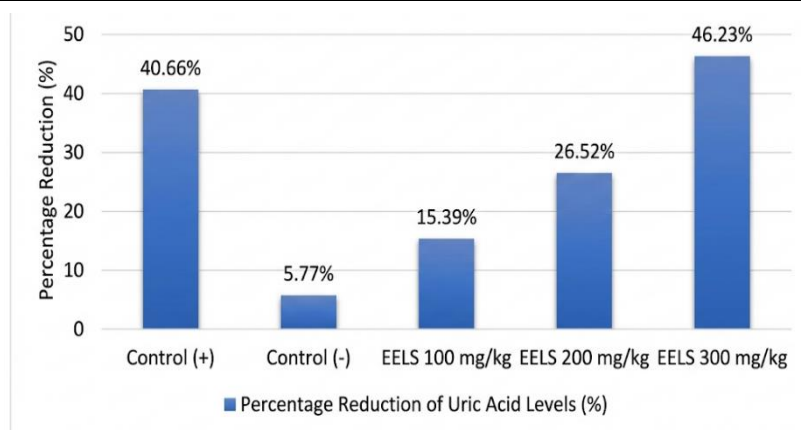
Pharmacy and Medical Devices (2017). This high yield indicates that *Sechium edule* has a rich secondary metabolite matrix that is easily extracted with polar solvents. Compared to studies on *Cucurbita maxima* (yellow squash), which has a yield value of around 25.08%, the 15.73% value for *Sechium edule* still indicates high efficiency considering the characteristics of this fruit, which has different water and fiber content (Vieira et al., 2019b; Grassino et al., 2024). The significance of 96% ethanol solvent is very strategic because it can optimally extract flavonoids (both in aglycone and glycoside forms), alkaloids, and saponins while minimizing the extraction of inactive long-chain polysaccharides, thereby increasing the specific bioactivity potential of the extract (Jabbari et al., 2024; Grassino et al., 2024; Shah et al., 2025)

### 3.2. Impact on Serum Uric Acid Levels

Potassium oxonate induction (Group II) significantly increased serum uric acid levels ( $p < 0.01$ ) compared to the normal control group (Group I) on days 7 and 14, confirming the hyperuricemia model used.

**Table 2.** Average Serum Uric Acid Levels (mg/dL) Over 14 Days of Treatment

| Group                      | Average serum uric acid levels (mg/dL) $\pm$ SD |                                             |                           | Percentage decrease in uric acid levels (%) |
|----------------------------|-------------------------------------------------|---------------------------------------------|---------------------------|---------------------------------------------|
|                            | Normal Uric Acid                                | Uric Acid After Induction Potassium oxonate | Uric acid after Treatment |                                             |
| Control +                  | 3.2 $\pm$ 0.05                                  | 6.5 $\pm$ 0.244949                          | 5.2 $\pm$ 0.594418        | 40.46% $\pm$ 17.14 <sup>b,c</sup>           |
| Control -                  | 3.1 $\pm$ 0.057735                              | 6.1 $\pm$ 0.170783                          | 5.9 $\pm$ 0.129099        | 5.77% $\pm$ 2.82 <sup>a,d,e</sup>           |
| EESE 100 mg/kg body weight | 3.2 $\pm$ 0.08165                               | 6.6 $\pm$ 0.23094                           | 6.0 $\pm$ 0.25            | 15.39% $\pm$ 4.01 <sup>a, e</sup>           |
| EESE 200 mg/kg BW          | 3.0 $\pm$ 0.05                                  | 5.4 $\pm$ 0.221736                          | 4.8 $\pm$ 0.330404        | 26.09% $\pm$ 27.2 <sup>b,e</sup>            |
| EESE 300 mg/kg BW          | 3.0 $\pm$ 0.05                                  | 5.5 $\pm$ 0.707107                          | 4.4 $\pm$ 0.685565        | 46.23% $\pm$ 14.4 <sup>3b,c,d</sup>         |

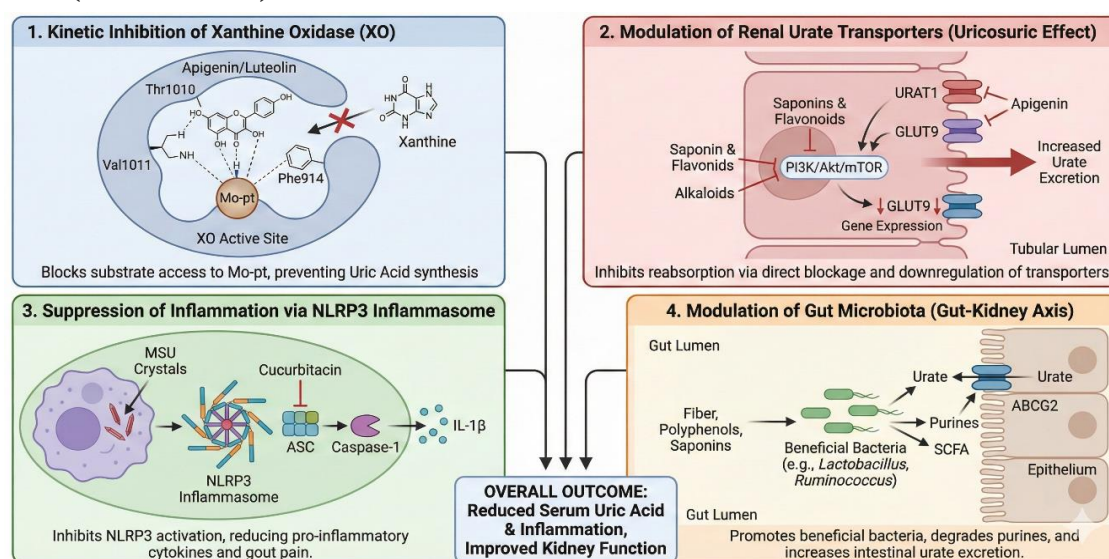


**Figure 3.** Percentage Reduction in Uric Acid Levels

Biological response of laboratory animals, namely mice (*Mus musculus*), to hyperuricemia induction using potassium oxonate. Potassium oxonate acts as an inhibitor of the hepatic uricase enzyme, preventing the conversion of uric acid into the more soluble allantoin, thereby successfully mimicking the physiological conditions of humans who lack active uricase enzyme (Abu-Gharbieh et al., 2019)(Rodríguez-Rovira et al., 2023). The results obtained showed a clear and progressive decrease in uric acid levels with increasing doses of EESE, an important characteristic indicating specific pharmacological interaction. A dose of 100 mg/kgBW extract resulted in a  $15.39\% \pm 4.01$  decrease in uric acid levels. This effect, although statistically significant compared to the negative control, represents the initial threshold of biological activity. In a therapeutic context, this level of reduction may be more useful in preventive strategies or adjuvant therapy than as monotherapy for acute cases. A dose of 200 mg/kgBW produced a significant increase in response with a reduction of  $26.09\% \pm 2.72$ . The stability of the response at this point (marked by a relatively small standard deviation) indicates a dose range ( ) with consistent effects. These findings suggest that the 200 mg/kgBW dose is within the range of linear pharmacologic effects and can be considered an effective therapeutic dose. The highest dose tested, 300 mg/kgBW, produced the most dramatic reduction, reaching  $46.23\% \pm 14.43$ . This magnitude not only approaches the effectiveness of the standard pharmacological agent (positive control, 40.46%) but also demonstrates strong inhibitory potential against the mechanism of hyperuricemia. Increased data variability at this dose, as seen in the larger standard deviation, may reflect individual variation in pharmacokinetics or approaches to saturation (*plateau effect*) of one or more drug action mechanisms. Siamese pumpkin is traditionally known as a diuretic vegetable. Its high potassium content and compounds such as saponins may increase *urine production* and renal clearance of uric acid by affecting electrolyte balance and possibly inhibiting uric acid reabsorption transporters in the renal tubules (Siahaan et al., 2021).

Phytochemical studies on *Sechium edule* consistently identify apigenin and luteolin as the dominant flavonoids (Vieira et al., 2019b). *In silico* and enzyme kinetics studies show that the planar structure of rings A and C in apigenin, as well as the C2=C3 double bond, allow apigenin to enter the XO catalytic pocket (Lin et al., 2015). Apigenin and luteolin form strong hydrogen bonds with key amino acid residues in the active site of XO, such as Thr1010, Val1011, and Phe914. These interactions stabilize the enzyme-inhibitor complex and prevent the substrate (*xanthine*) from accessing the molybdenum center, thereby effectively inhibiting uric acid synthesis (Altunayar-Unsalan & Unsalan, 2024). The flavonoid fraction of *Sechium*

edule has a competitive  $IC_{50}$  against XO, and in some cases even shows higher binding affinity than febuxostat in *docking* simulations (Peanlikhit et al., 2025). The ability of EESE 300 mg/kgBW to be more effective than allopurinol is most likely due to an additional effect on the kidneys, namely the inhibition of uric acid reabsorption. Approximately 90% of uric acid filtered by the kidneys is reabsorbed back into the blood by the URAT1 (*SLC22A12*) and GLUT9 (*SLC2A9*) transporters in the proximal tubules (Wagner, 2025)(Liu et al., 2025). Apigenin in Siam pumpkin ethanol extract acts as a competitive inhibitor of GLUT9. Apigenin occupies the substrate binding site in the *open* conformation of the transporter, physically blocking the movement of urate from the tubule lumen back into the epithelial cell (Shen et al., 2024). In addition to physical blockade, triterpenoid saponins (such as *cucurbitacin*) and flavonoids have been shown to reduce the expression of URAT1 and GLUT9 mRNA and proteins in hyperuricemic animal models (Zhu et al., 2017). This reduces the kidney's ability to retain uric acid, thereby increasing its excretion via urine (uricosuric effect). Alkaloids detected in EESE also play a role in inhibiting the PI3K/Akt/mTOR signaling pathway that regulates urate transporter expression, providing an additional layer of mechanism in promoting urate excretion (Li et al., 2024).

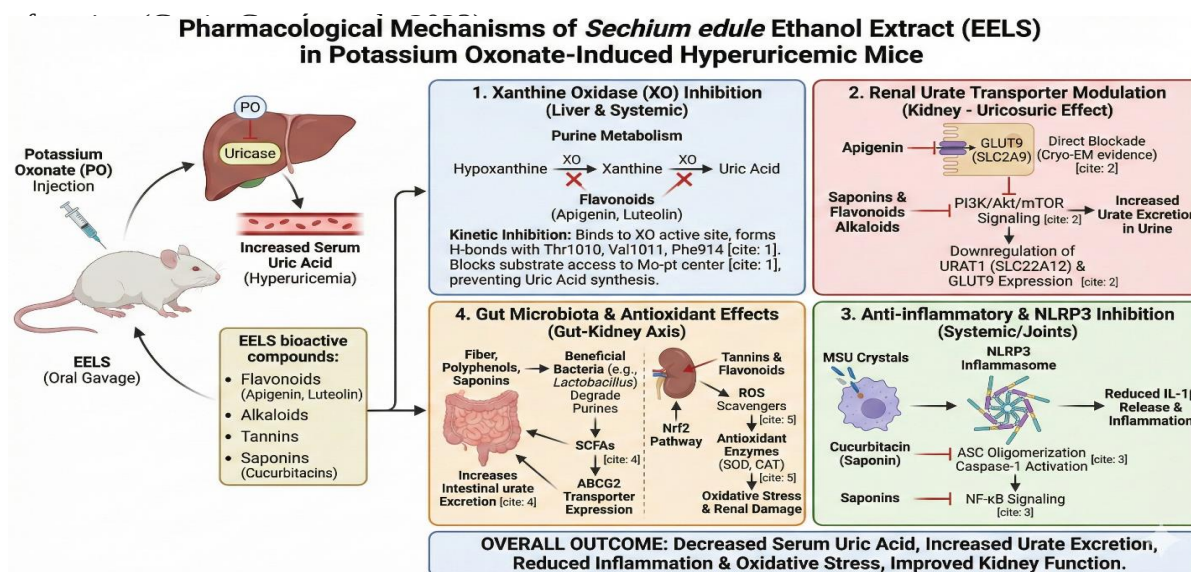


**Figure 4.** Integrated pharmacological pathways of phytochemical compounds in uric acid regulation and anti-inflammatory response.

Note: Image generated by Google Gemini 1.5 Pro based on the author's descriptive prompt [Generate a comprehensive medical infographic titled 'Multitarget Mechanisms of Phytochemicals in Gout Management' consisting of four quadrants connected to a central summary box. Quadrant 1: Illustrate the kinetic inhibition of the active site of Xanthine Oxidase (XO) by Apigenin/Luteolin, showing molecular interactions with Thr1010, Val1011, and Phe914, which block substrate access to the Mo-pt center. Quadrant 2: Illustrate the modulation of renal urate transporters (URAT1, GLUT9) by Saponins and Flavonoids, highlighting the PI3K/Akt/mTOR pathway and decreased GLUT9 gene expression in the tubular lumen. Quadrant 3: Show the suppression of the NLRP3 inflammasome by Cucurbitacin, inhibiting ASC and Caspase-1 activation to reduce IL-1 $\beta$  release from MSU crystals. Quadrant 4: Illustrate the modulation of the gut-kidney axis by fiber and polyphenols, promoting beneficial bacteria (*Lactobacillus*, *Ruminococcus*) and urate excretion mediated by ABCG2. Center Box: Conclusion with 'OVERALL RESULTS: Reduction in Serum Uric Acid & Inflammation, Improvement in Kidney Function'. Use a professional academic layout with clean diagrams, clear labels, and Times New Roman font.], by Google, 2024 (<https://gemini.google.com/>).

Chronic hyperuricemia triggers the formation of MSU crystals, which are recognized by

the innate immune system as a *danger signal*, activating the NLRP3 inflammasome protein complex. This activation triggers the release of the pro-inflammatory cytokine IL-1 $\beta$ , causing severe pain during gout attacks. *Sechium edule* is rich in cucurbitacins (types B, E, I) (Li et al., 2024b). Cucurbitacin B has been identified as a specific and potent inhibitor of NLRP3 inflammasome activation. Its mechanism involves inhibiting the oligomerization of the ASC adaptor protein and preventing the activation of Caspase-1 (Li et al., 2024b). By inhibiting NLRP3, EESE not only lowers uric acid levels but also prevents inflammatory complications (gouty arthritis). This provides a therapeutic advantage over pure uric acid-lowering drugs that lack intrinsic anti-inflammatory effects. The saponins in EESE enhance this effect by suppressing the NF- $\kappa$ B signaling pathway, reducing the production of pro-inflammatory cytokines (X. Lin et al., 2023). Hyperuricemia is often associated with gut dysbiosis (bacterial imbalance). The fiber, polyphenol, and saponin content in EESE can act as prebiotics, modulating the composition of the gut microbiota (Cui et al., 2025). EESE has the potential to increase the population of beneficial bacteria (such as *Lactobacillus* and *Ruminococcus*) that are capable of degrading purines and nucleosides in the intestine before they are absorbed, as well as increasing the expression of the ABCG2 excretion transporter in the intestinal epithelium through the production of short-chain fatty acids (SCFA) (Lu et al., 2025). The tannin and flavonoid content in EESE acts as an electron donor, neutralizing ROS and breaking the chain of free radical oxidation reactions. *Sechium edule* has been reported to activate the transcription factor Nrf2, the main regulator of cellular antioxidant defense. This activation increases the expression of endogenous antioxidant enzymes ( , Catalase), protects renal nephrons from oxidative damage due to hyperuricemia, and maintains optimal renal filtration



**Figure 5.** Pharmacological mechanism of *Sechium edule* in a hyperuricemic micemodell.

Note: Image generated by Google Gemini 1.5 Pro based on the author's descriptive prompt ["Generate a highly detailed pharmacological infographic entitled 'Pharmacological Mechanisms of Sechium edule Ethanol Extract (EELS) in Potassium Oxonate-Induced Hyperuricemic Mice'." The visual should include a flowchart starting with 'Potassium Oxonate Injection (PO)' leading to the mouse model with 'Increased Serum Uric Acid'. Include four main mechanism panels: (1) Xanthine Oxidase (XO) Inhibition: showing flavonoids (Apigenin, Luteolin) bound to the active site of XO at Thr1010, Val1011, and Phe914. (2) Renal Urate Transporter Modulation: depicting decreased expression of URAT1 and GLUT9 via PI3K/Akt/mTOR signaling. (3) Anti-inflammatory & NLRP3 Inhibition: depicting suppression of MSU crystals and reduced IL-1 $\beta$  release by saponins (Cucurbitacins). (4) Gut Microbiota & Antioxidant Effects: displays the 'Gut-Kidney Axis', SCFAs, and the Nrf2 pathway.]. Use a professional academic layout with clean diagrams, clear labels, and Times New Roman font.], by Google, 2024 (<https://gemini.google.com>).

#### 4. CONCLUSION

Based on the results obtained, ethanol extract of *Sechium edule* Sw. fruit (EESSE) was found to have antihyperuricemic activity in male white rats induced with potassium oxonate. At a dose of 400 mg/kgBW, this extract was able to reduce serum uric acid levels with efficacy comparable to allopurinol 10 mg/kgBW. This activity is strongly suspected to be related to its ability to inhibit the xanthine oxidase enzyme in the liver, with an inhibition percentage of 47.5%. EESSE also has the potential to repair kidney tissue damage caused by hyperuricemia. However, this study did not include long-term toxicity testing or more in-depth molecular analysis, so these results need to be further examined before they can be widely applied.

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