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Original Research

Anti-hyperuricemia effect of ethanol and n-hexane fractions of celery leaf and stem in Wistar rats

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Abstract: This study investigated the antihyperuricemic effects of ethanol and n-hexane fractions derived from celery (*Apium graveolens* L.) leaves and stems in potassium oxonate-induced Wistar rats. Celery plant materials were subjected to extraction and subsequent fractionation using ethanol and n-hexane. Phytochemical profiling using gas chromatography–mass spectrometry (GC–MS) identified the presence of phenolic compounds across all fractions. Serum uric acid levels were measured before and after induction, followed by treatment with allopurinol and the respective celery fractions. Statistical analysis revealed significant differences in uric acid levels among treatment groups after intervention. In vitro xanthine oxidase (XO) inhibition was assessed using UV–Vis spectrophotometry, with allopurinol demonstrating the highest inhibitory activity, followed by the ethanol fraction of celery stems. Histopathological evaluation of renal tissues showed glomerular necrosis in the untreated hyperuricemic group, while varying degrees of renal damage persisted in groups treated with celery fractions, particularly at higher doses of leaf extracts. Overall, the findings suggest that ethanol and n-hexane fractions of celery possess antihyperuricemic potential, likely mediated through XO inhibition, although their renal protective effects appear limited under the conditions tested.

Keywords: xanthine oxidase inhibition; histopathology; ethanol fraction; n-hexane fraction; celery leaves; celery stems; uric acid.

INTRODUCTION

Hyperuricemia is a metabolic disorder characterized by elevated serum uric acid levels, leading to Gout Arthritis due to monosodium urate crystal deposition.[1,2] Additionally, it may contribute to kidney stones or kidney damage over time. Factors like a purine-rich diet, alcohol consumption, obesity, and genetics can trigger hyperuricemia.[3] Treatment involves lifestyle adjustments, such as adopting a low-purine diet, limiting alcohol, and maintaining a healthy weight.[4] While current treatments like Allopurinol are effective Xanthine Oxidase (XO) inhibitors, they are associated with adverse effects such as hypersensitivity and hepatotoxicity.[5] Consequently, herbal alternatives like Celery (Apium graveolens L.) are being explored.[6,7]

Celery (*Apium graveolens L.*) has been studied for its bioactivity and potential health benefits.[8] The celery seed aqueous extract and celery seed oil extract in rodent models showed anti-gout effects by suppressing serum uric acid levels in mice with hyperuricemia and the swelling rates of ankle joints in rats with gouty arthritis.[9] But the previous study did not determine which extract exhibited stronger effects, and which component exhibited the anti-gouty arthritis and anti-hyperuricemia properties. A study has demonstrated that celery has high levels of phenolic compounds and flavonoids,[10] exhibiting significant antioxidant and free

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radical scavenging activities in vitro.[11] Current literature studies revealed that celery has a beneficial effect on hypertension[12], hyperglycemia[13], and hyperlipidemia.[14] The bioactive ingredients in celery extract have shown hypolipidemic, antidiabetic, and hypotensive properties.[8,15] The therapeutic effects are attributed to flavonoids due to their enzyme inhibitory and antioxidant activities.[16] Celery contains phytochemicals such as phenolic acids, flavones, and flavonols,[11] and antioxidants such as vitamin C, beta-carotene, and manganese, which have a role in decreasing oxidative damage and inflammation.[17]

While traditional urate-lowering therapies (ULT) effectively inhibit XO, their clinical utility is often limited by severe adverse effects such as allopurinol hypersensitivity syndrome and cardiovascular risks associated with febuxostat.[18,19] Consequently, there is an urgent need for the development of novel, safer drug candidates with high efficacy and minimal toxicity.[20,21] Recent advancements in medicinal chemistry have highlighted natural active substances, particularly flavonoids, as promising alternatives due to their multi-target mechanisms that regulate both uric acid production and renal excretion.[22] Cutting-edge research is even utilizing near-infrared spectroscopy and green metal-organic frameworks (MOFs) to rapidly predict the dual-enzyme inhibitory activity of these natural compounds against XO.[23]

However, significant scientific uncertainty remains regarding the comparative efficacy of different plant parts. Specifically, no study has directly compared the antihyperuricemic effects of ethanol versus n-hexane fractions between the leaf and stem parts of A. graveolens, nor evaluated their potential renal-protective effects in a potassium-oxonate hyperuricemia model.[24] Furthermore, the correlation between specific bioactive compounds in these fractions and their in vivo XO inhibitory mechanism remains underexplored. This study aims to fill this gap by identifying the most potent fraction and validating its mechanism of action and safety profile. This study might contribute to the understanding of the pharmacological effect of celery extract on lowering uric acid levels, xanthine oxidase inhibition as well as pathological renal tissues.

MATERIALS AND METHOD

We used instruments of ELISA kit with 96 wells and 450 ± 10 nm filter, XOD kit, UV-vis spectrophotometer, rotary evaporator, freeze dryer, and centrifuge 4000 rpm. Celery leaves and stems were collected from the traditional market in Medan, North Sumatra.

About 1000 g of each leaf and stem part of the celery plant were macerated in 10 L ethanol 96% until thick extract was obtained after rotary evaporation. About 20 g of thick extract was added with 40 mL ethanol, then added 100 ml of hot water, then fractionated with 100 mL of n-hexane in a separatory funnel.

Phytochemical profiling of leaves and stem were performed using Gas Chromatography-Mass Spectrometry (GC-MS) to identify bioactive compounds. Column type, HP-5MS, Carrier gas Helium at 1 mL/min, Injection temp 250°C.

The leaves and stem extracts were then also examined for xanthine oxidase inhibition by using a UV-vis spectrophotometer. Procedures for preparing xanthine substrate and allopurinol solutions as well as enzyme activity inhibition were referred to the established protocols. The reaction mixture consisted of 1 mL of enzyme solution (0.1 units/mL in 0.05 M Phosphate Buffer, pH 7.5) and 2 mL of Xanthine substrate. The mixture was pre-incubated at 37°C for 10 minutes, followed by the addition of the test extract. After 30 minutes of incubation, the reaction was stopped with 1 mL of 1 N HCl. Absorbance was measured at 290 nm.

Animal experiments were 45 individuals of healthy male Wistar rats with 250-300 g of body weight (bw) and 3 months. Animals were divided into 7 groups; (1) standard or normal treatment, (2) negative control with potassium oxonate

(PO), (3) positive control with PO + allopurinol, (4) treated with PO + n-hexane stem extract, (5) treated with PO + ethanol stem extract, (6) treated with PO + n-hexane leaves extract, (7) treated with PO + ethanol leaves extract. All groups and sub-group in this experiment were three individuals. All treatment groups were induced by potassium oxide 250 mg/kg bw which was injected via intraperitoneal and given allopurinol 9 mg/kg bw in PGA 3% w/v with a volume of 1 ml/100 g bw administration. Each of groups 4,5,6, and 7 was sub-grouped into three dose variations. Doses were calculated based on the crude extract mass: Dose I (1 g/kg BW), Dose II (1.5 g/kg BW), and Dose III (2 g/kg BW). The extracts were suspended in 0.5% CMC-Na and administered orally at a volume of 10 mL/kg BW.

Furthermore, the animals were examined for uric acid levels before and after the induction of potassium oxonate and the treatment on days 14th and 28th. On day 29th, all animals were killed by euthanasia. Then the kidney organs were taken to make histological preparations and interpretation using an electron microscope by an anatomical pathologist. The animal experimental method in this research has been approved by Komisi Etik Penelitian Kesehatan UNPRI no. 010/KEPK/UNPRI/VIII/2022.

Kidney tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 6 µm, and stained with Hematoxylin and Eosin (H&E). Damage was quantified using a semi-quantitative scoring system:

- **Score 0:** Normal
- **Score 1:** Mild (Focal damage)
- **Score 2:** Moderate (Multifocal damage)
- **Score 3:** Severe (Diffuse damage) Parameters assessed included tubular necrosis, inflammatory infiltration, and glomerular edema.

Data were analyzed using SPSS software (Version 25). Normality was verified using the Shapiro-Wilk test and homogeneity using Levene's test. Differences between groups were assessed using One-Way ANOVA followed by LSD (Least Significant Difference) post-hoc test. A p-value < 0.05 was considered statistically significant.

RESULTS

Phytochemical Profiling (GC-MS)

GC-MS analysis revealed distinct profiles for leaf and stem fractions. The ethanol stem fraction was dominated by *Neophytadiene, n-Hexadecanoic acid,* and *3-Butylisobenzofuran-1(3H)-one*, which are known for their antioxidant properties. In contrast, the n-hexane fractions contained higher levels of fatty acid methyl esters (FAMEs) as presented in Supplementary Materials Table 1..

Uric Acid Levels

Induction with potassium oxonate significantly increased serum uric acid levels in the positive control group ($p < 0.001$). Treatment with the Ethanol Leaf Fraction (Dose III) showed the most significant reduction in uric acid levels on Day 28, comparable to the standard drug Allopurinol ($p > 0.05$ vs Allopurinol) as presented in Figure 1.

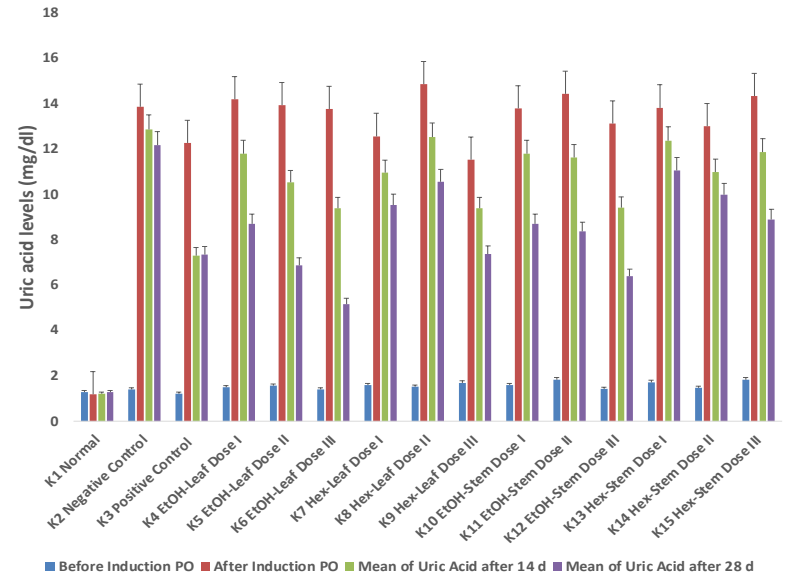


Figure 1. Mean values of uric acid levels of all groups.

All treated groups showed normal distribution and homogenous data before and after treatments. ANOVA resulted in significant differences between groups before and after treatments ($p < 0.05$).

Xanthine Oxidase Activity

The in vitro assay demonstrated that the Ethanol Stem Fraction exhibited the strongest XO inhibition with an IC_{50} of 8.25 µg/mL, followed by the Ethanol Leaf Fraction (IC_{50} = 27.81 µg/mL). Allopurinol served as the positive control (IC_{50} = 0.58 µg/mL). Data of xanthine oxidase activity in-vitro is presented in Table 2.

Table 1. Inhibition of Xanthine Oxidase and IC_{50} values.

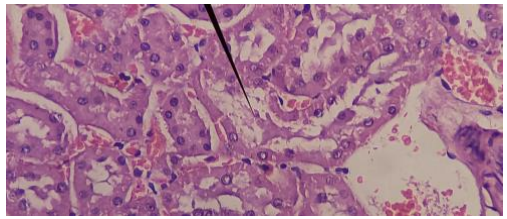
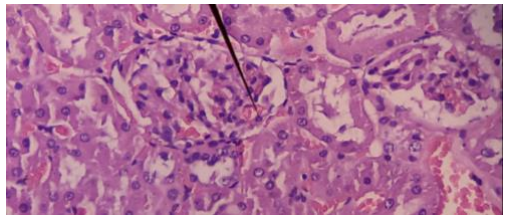
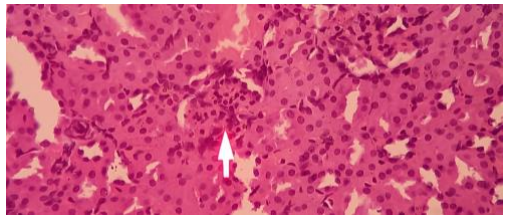
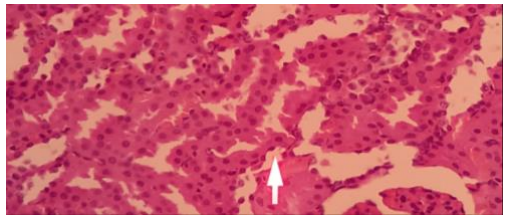
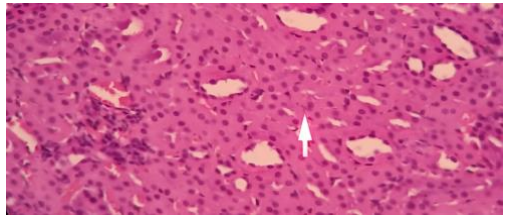
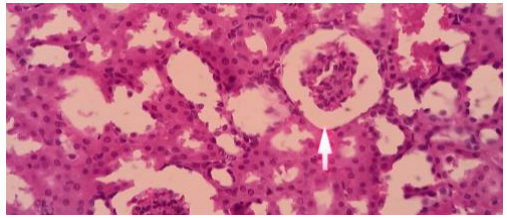
Sample	Inhibition of XO (%)	IC_{50}
Allopurinol	78.00	0.58
Ethanol fraction of leaves	1.63	27.81
Ethanol fraction of stem	5.49	8.25
n-Hexane fraction of leaves	4.29	10.57

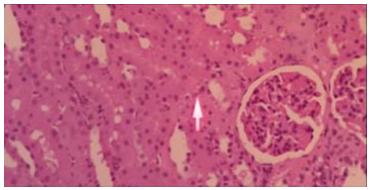
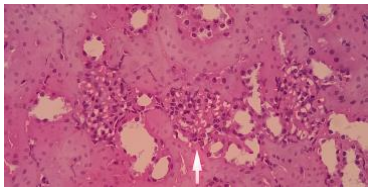
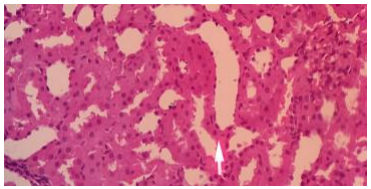
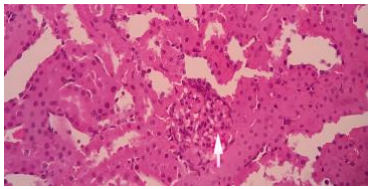
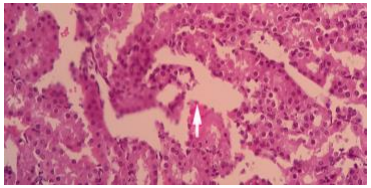
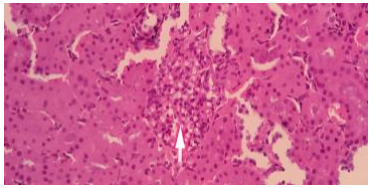
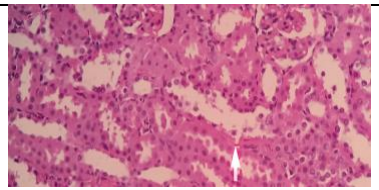
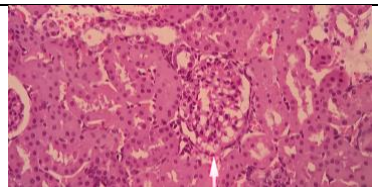
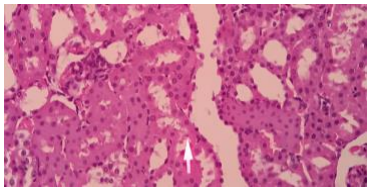
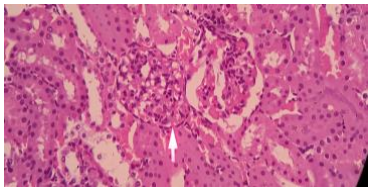
Due to technical reasons, we can not provide the data on the n-Hexane fraction of the stem. However, the data in Table 1 clearly showed that the percentage of xanthine oxidase inhibition and IC_{50} values are not at the same level as commercial medication, allopurinol.

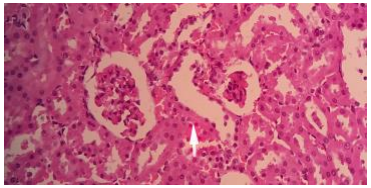
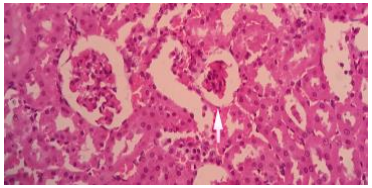
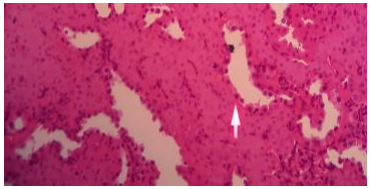
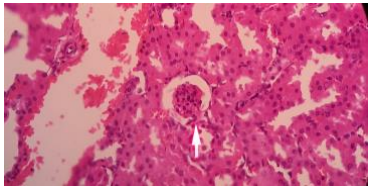
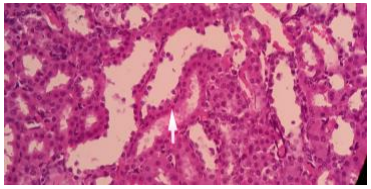
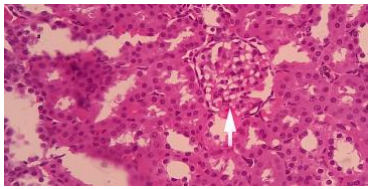
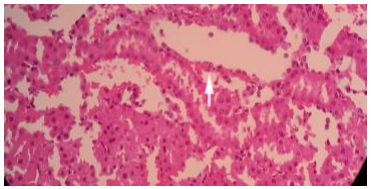
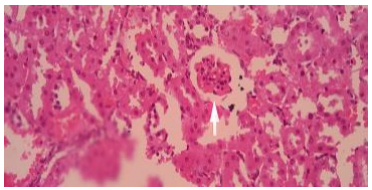
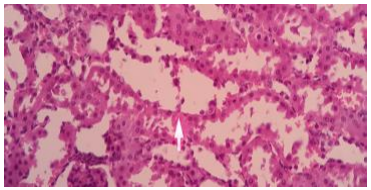
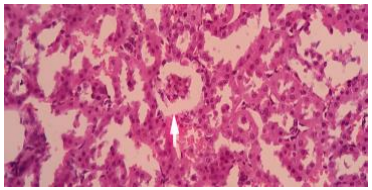
Histopathology of Renal Tissues

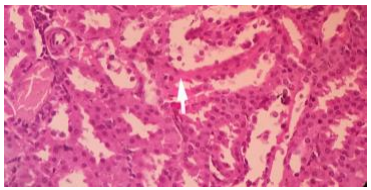
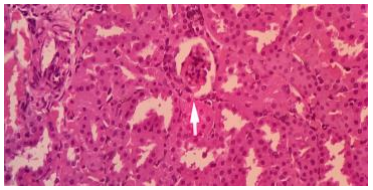
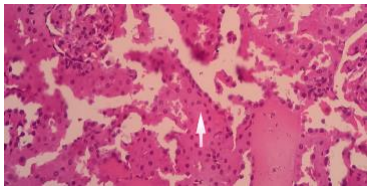
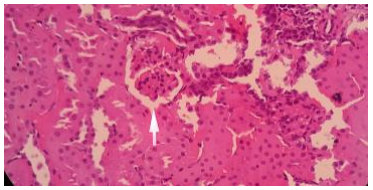
Histological analysis revealed varying degrees of renal damage (Table 2). While the control group showed normal architecture (Score 0), the induced group exhibited severe tubular necrosis and glomerular congestion (Score 3). Treatment with celery extracts provided partial protection, with lower doses showing mild improvement (Score 2), though higher doses in the leaf fraction did not significantly reverse damage.

Table 2. Histology pictures of renal tissues of all groups.

Groups	Pictures of Tubules	Dilatation	Intertubular boundaries	Pictures of Glomerulus	Damages
K1		1	0		1
K2		0	1		1
K3		1	1		2

	Dose I		1	0		2
K4	Dose II		1	0		1
	Dose III		1	0		2
	Dose I		1	0		2
K5	Dose II		1	0		2

	Dose III		2	0		3
K6	Dose I		2	2		3
	Dose II		2	2		2
	Dose III		2	1		2
K7	Dose I		3	1		3

Dose II		1	1		2
Dose III		2	0		2

DISCUSSION

Celery leaves and stems were suggested to reduce uric acid levels because of their phenolic and flavonoid compounds.[25] Celery leaves, stems, and seeds contain furocoumarins (apigravin, celerin, and umbelliferone), flavonoids (apigenin, apiin, kaempferol, and luteolin), phenolic compounds (caffeic acid, p-coumaric acid, and ferulic acid), and tannins.[26] Another study also reported the presence of phenolic compounds in the ethanol extract of celery stems.[27] A high phenolic content is also found in celery extract instead of tannins, saponins, and steroids. However, no terpenoid has been reported.[28]

The data presented in Figure 1 has indicated that celery leaf and stem extracts could reduce uric acid levels after the 14th and 24th days of treatment. To compare the significance between groups of treatments, the post-hoc (LSD) test showed the K3> K6> K12 = K13> K4 = K5 = K7 = K8 = K9 = K14 > K15 >K10 consecutively. This analysis mentioned that the strongest effect was the Positive Control group then followed by the Ethanol Fraction of Leaf Dose III as the best treatment of celery extract. Our result has conformity with the previous report that the strongest effect was the leaf extract of celery.[25]

The phenolic compound was responsible for reducing uric acid levels through xanthine oxidase inhibition.[29] The mechanism was by suppressing O^{2-} generation, and scavenging O^{2-} and DPPH radicals. The inhibitory mechanism was derived into three types of reactions. The first is xanthine oxidase inhibition, the second is suppression of O^{2-} generation by modification of the enzyme molecule and the third is two forms of O^{2-} transport. Those reactions were related to the arrangement of the hydroxyl groups on the phenol moiety and the alkenyl chain that plays a key role in the inhibition effect of xanthine oxidase.[30] In addition, kaempferol, another flavonoid found in celery, inhibits xanthine oxidase reversibly by occupying the catalytic center of the enzyme.[17]

A previous study on the XO inhibition effect of celery stems water infusion extract showed a better effect compared to celery leaves at a concentration of 20%.The inhibition type testing of celery stem extract showed an uncompetitive type of inhibition after the addition of extracts. Other research on the hydroalcoholic extracts from A. graveolens against potassium oxonate (PO)-induced hyperuricemia rats lowering the uric acid level via inhibition of hepatic xanthine dehydrogenase (XDH) and XO.[26] Low effects on the enzyme activity and antioxidant level in our study might be due to the impurities of the thick extract used, and some technical issues, hence the data obtained based on the UV-vis spectra did not show rigorous results. Otherwise, we could see that the ethanol fraction of stem indicated the highest inhibition effect among treatment groups with 5.49% of XO inhibition and IC_{50} of 8.25 µg/mL.

This study demonstrates that ethanol fractions of A. graveolens are more effective than n-hexane fractions in reducing uric acid levels, likely due to the higher solubility of polar flavonoids like apigenin and luteolin which act as competitive inhibitors of Xanthine Oxidase. Our results indicate a discrepancy between in vitro and in vivo efficacy. While the Stem Ethanol fraction was the most potent XO inhibitor in vitro (IC50 8.25 µg/mL), the Leaf Ethanol fraction proved more effective in reducing serum uric acid in rats. This suggests that the leaf extract may operate via dual mechanisms: inhibiting XO production (confirmed by the presence of Neophytadiene and flavonoids) and potentially enhancing renal uric acid excretion, a pathway not captured by the in vitro enzyme assay.

Generally, histology data showed no improvement in the kidney damage that occurred despite being treated with herbal celery leaves and stems. there may be no improvement in the structure of the kidney due to differences in the inducing substances (potassium oxonate) that cause irreversible kidney damage and or the

toxic effects of celery leaves and stems and or inadequate doses of celery given. Our result was in line with the study reported that celery leaf extract given orally can reduce microscopic damage to rat kidney tubules induced by a hypercholesterolemia diet. Furthermore, higher concentrations also contribute to the acute toxicity effect of celery extract on the renal histology properties of the Sprague Dawley rat model.[31]

Contrary to the expectation of complete renal protection, high doses of leaf extract did not fully reverse glomerular necrosis. This observation aligns with reports that concentrated celery extracts may contain furocoumarins, which can exhibit nephrotoxicity at high concentrations.[32] This suggests a therapeutic window where celery is effective for hyperuricemia but requires careful dosing to avoid exacerbating renal stress.

Limitations and Future Directions:

This study had a limited sample size (n=3 per subgroup), which may affect statistical power. Additionally, the in vitro data for the n-hexane stem fraction was incomplete. Future studies should focus on isolating specific flavonoids from the ethanol fraction to validate the molecular mechanism and conducting pharmacokinetic studies to determine the optimal safety margin.

CONCLUSION

In conclusion, ethanol and n-hexane fractions of celery (*Apium graveolens* L.) leaves and stems contain phenolic compounds and exhibit anti-hyperuricemic activity in potassium oxonate-induced Wistar rats. Allopurinol demonstrated the strongest uric acid–lowering effect, while ethanol fractions of celery showed moderate activity. The ethanol stem fraction exhibited the highest xanthine oxidase inhibitory activity in vitro, whereas the ethanol leaf fraction showed greater efficacy in reducing serum uric acid levels in vivo, suggesting possible differences in underlying mechanisms. Histopathological findings indicated that celery fractions provided limited renal protection, with residual tissue damage observed in several treatment groups, particularly at higher doses. Overall, these findings suggest that celery extracts may serve as potential natural anti-hyperuricemic agents, primarily through xanthine oxidase inhibition, although additional mechanisms may also contribute. Further studies are required to clarify these mechanisms, optimize dosing, and evaluate their safety and efficacy in more robust experimental settings.

AUTHORS' CONTRIBUTIONS

Agnes Fany Cahyani Hura: Methodology, Software, Formal Analysis, Investigation, Resources, Data Curation, Visualization, Writing-Original Draft. Refi Ikhtiari: Conceptualization, Validation, Resources, Writing-Review&Editing, Supervision, Project Administration. Maya Sari Mutia: Conceptualization, Validation, Resources, Supervision, Project Administration.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author upon reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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