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NEPHROPROTECTIVE EFFECTS OF CELERY EXTRACT (APIUM GRAVEOLENS L.) ON UNILATERAL URETERAL OBSTRUCTION MODELS

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ABSTRACT
Renal fibrosis represents the final pathological endpoint of chronic kidney injury, characterized by excessive extracellular matrix deposition and irreversible structural damage, ultimately leading to end-stage kidney disease (ESKD) necessitating renal replacement therapy. Given the largely irreversible nature of established fibrosis, current therapeutic approaches primarily aim to suppress fibrogenesis and delay further renal deterioration. Celery (Apium graveolens L.) contains bioactive compounds with potential nephroprotective properties. Unilateral ureteral obstruction (UUO) is a well-established experimental model of renal fibrogenesis, in which persistent obstruction leads to tubular injury and activation of profibrotic signaling pathways. This study aimed to evaluate the nephroprotective effect of celery ethanol extract on renal injury in UUO rat model. A post-test-only control group design was conducted using 25 rats randomly assigned into five groups: sham control, negative control (UUO), and three treatment groups receiving celery extract (125, 250, and 500 mg/kg body weight) for 14 days. Serum creatinine levels were measured from blood samples, while renal tubular injury scores were assessed through histopathological examination of kidney tissues. One-way ANOVA followed by a least significant difference (LSD) post hoc test revealed significant differences among groups ($p < 0.05$), with the 250 mg/kg dose showing the most pronounced effect, suggesting potential nephroprotective activity. These findings necessitate further investigations, including toxicity assessment and clinical studies, to establish its therapeutic applicability.

Keywords: celery; phytopharmaca; renal fibrosis; unilateral ureteral obstruction

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INTRODUCTION

Chronic kidney disease (CKD) is clinically defined as a persistent decline in renal function lasting more than three months. Within the Indonesian population aged 15 and older, the incidence of CKD escalated from 0.2% in 2013 to 0.38% by 2018 On a global scale, the condition impacts approximately 10% of individuals, with the disease burden steadily expanding due to an aging demographic and associated health risks (Panizo et al., 2021). The terminal stage of CKD is marked by renal fibrosis, a pathological state involving excessive extracellular matrix deposition and permanent structural degeneration that eventually culminates in end-stage kidney disease (ESKD). This fibrotic progression is facilitated by chronic inflammatory responses, urinary tract obstructions, and metabolic conditions such as diabetes and hypertension, all of which catalyze ongoing fibrogenesis (Chevalier, 2016; Gu et al., 2020). Currently, no definitive therapy exists to reverse renal fibrosis and treatment remains limited to renal replacement therapies, including dialysis and kidney transplantation. Therefore, strategies targeting fibrogenesis are essential to delay disease progression. In this regard, traditional medicine and phytopharmaceuticals have gained increasing attention as potential alternatives due to their accessibility, favorable safety profile, and cost-effectiveness (Katzung et al., 2017).

Apium graveolens L., commonly referred to as celery, is a frequently utilized botanical with documented medicinal utility. Its complex chemical profile comprises a broad spectrum of bioactive secondary metabolites, notably phenolics, flavonoids, steroids, furocoumarins, volatile oils, and sesquiterpene alcohols (Afifah et al., 2019; Khairullah et al., 2021). Flavonoids, in particular, are lauded for their substantial antioxidant efficacy; they function by sequestering free radicals and stimulating endogenous protective enzymes, such as glutathione S-transferase, thereby limiting oxidative harm to renal parenchyma. Beyond these actions, celery exhibits diuretic and anti-inflammatory properties and has been cited for its role in promoting the breakdown of renal and biliary stones (Aulia et al., 2019). Moreover, experimental evidence from chronic kidney disease rat models has demonstrated that celery ethanol extract, administered at dosages of 250 and 300 mg/kg body weight, effectively mitigated elevations in serum urea and creatinine, thereby illustrating its prospective nephroprotective capacity (Afifah et al., 2020).

Unilateral ureteral obstruction (UUO) is a widely recognized experimental model that effectively simulates the pathological processes of obstructive renal conditions, including those caused by ureteral calculi, trauma, strictures, and malignancies (Hammad, 2022). Persistent obstruction leads to renal ischemia and hypoxia, which subsequently trigger progressive structural damage, functional decline, and eventual progression to end-stage kidney disease (ESKD) (Susanto et al., 2019). In experimental settings, UUO induction in rats, typically performed under ketamine anesthesia, results in pronounced renal injury characterized by inflammation and oxidative stress. This oxidative stress arises from an imbalance between insufficient antioxidant defenses and excessive production of reactive oxygen species, leading to enhanced free radical activity and impaired endogenous antioxidant enzyme function. Consequently, these processes exacerbate cellular injury and are associated with molecular alterations, including N-carboxymethyl-lysine (CML) accumulation, amino acid modifications, and disruption of basement membrane integrity (Martínez-Klimova et al., 2019).

Given the central role of oxidative stress in UUO-induced renal injury and fibrogenesis, therapeutic strategies targeting oxidative imbalance are of considerable interest. In this regard, Apium graveolens L. has demonstrated notable antioxidant properties. Previous studies have reported that celery extract exhibits significant antioxidant activity at doses of 100 and 200 mg/kg body weight (Khairullah et al., 2021). Furthermore, administration of celery ethanol extract at 250 mg/kg body weight has been shown to preserve antioxidant defenses—such as superoxide dismutase (SOD) and glutathione (GSH)—while reducing lipid peroxidation markers, including malondialdehyde (MDA), in experimental models of chronic kidney disease (Afifah et al., 2022). However, the specific nephroprotective capacity of celery extract within the UUO framework had not been previously investigated. Consequently, the current study was designed to assess the efficacy of celery ethanol extract at dosages of 125, 250, and 500 mg/kg body weight in attenuating renal injury in UUO rats, utilizing serum creatinine and histological tubular injury scores as primary metrics.

METHOD

Method Types of Research

This study employed a laboratory-based experimental design with a post-test-only control group approach to evaluate the nephroprotective effects of celery extract in a unilateral ureteral obstruction (UUO) rat model. The study was conducted from June to September 2022 at the Research Laboratory and the Pharmacology Laboratory, Faculty of Medicine, Universitas Jenderal Soedirman. The materials and instruments used in this study included Sprague Dawley rats, *Apium graveolens* L. (celery), AD2 standard rodent feed, ketamine, 70% ethanol, hematoxylin–eosin staining reagents, 3/0 silk sutures, povidone-iodine, minor surgical instruments, syringes, sterile gloves, sample containers, pipettes, glass slides and coverslips, and a light microscope. This study employed a quantitative laboratory-based experimental design. Ethical clearance was granted by the Medical Research Ethics Committee, Faculty of Medicine, Universitas Jenderal Soedirman,

Purwokerto, Indonesia (No. 007/KEPK/PE/VIII/2022). A total of 25 male Sprague Dawley rats, aged 2–3 months and weighing 150–250 g, were included in accordance with the Federer formula. Prior to group allocation, all animals were acclimatized for 7 days under standard conditions with unrestricted access to food and water. The animals were randomly assigned into five groups. Group A (sham control) underwent surgical exposure without UUO induction or treatment. Group B (negative control) underwent UUO without celery extract. Groups C–E underwent UUO followed by administration of ethanol extract of *Apium graveolens* L. at doses of 125, 250, and 500 mg/kg body weight, respectively, for 14 days. On day 15, blood samples were collected prior to animal termination for kidney tissue harvesting. All procedures were performed under ketamine anesthesia, followed by euthanasia via cervical dislocation. Experimental work was conducted at the Pharmacology Laboratory, Faculty of Medicine, Universitas Jenderal Soedirman. To ensure statistical validity, the sample size was determined using Federer's formula, $(t-1)(n-1)>15$, where t represents the five treatment cohorts,. The resulting calculation indicated a minimum requirement of more than 4.75 subjects per group, which was subsequently rounded up to five. Consequently, each of the five experimental groups comprised five rats, reaching an aggregate sample size of 25 animals.

Preparation of *Apium graveolens* L. Extract

The *Apium graveolens* L. specimens were harvested from Pratin, Purbalingga, Central Java. Following an initial cleaning process involving washing and air-drying, the botanical material was oven-dried at 60°C until a stable weight was achieved to ensure complete moisture removal. The dehydrated plants were then pulverized into a fine powder. A 250 g portion of this powder was subjected to maceration in 70% ethanol using a 10:1 solvent-to-sample ratio for a total of 72 hours. To maximize extraction efficiency, the solvent was refreshed every 24 hours. Finally, the resulting filtrate was concentrated via a rotary evaporator to yield the crude ethanol extract required for experimental use.

Induction of Unilateral Ureteral Obstruction

The induction of unilateral ureteral obstruction (UUO) was achieved via surgical ligation of the left ureter. Following a midline abdominal incision to facilitate ureteral exposure, the proximal and distal segments of the left ureter were double-ligated using 3/0 silk sutures, after which the ureter was completely transected between the points of ligation. To minimize the risk of postoperative infection, the peritoneal cavity was irrigated with sterile normal saline (NaCl) prior to anatomical closure. The surgical site was subsequently closed using 4/0 silk sutures, followed by the topical application of povidone-iodine for antiseptic prophylaxis. Upon completion of the procedure, the animals were returned to solitary cages for postoperative recovery.

Serum Creatinine Assessment

To assess renal function, serum creatinine levels were measured upon the conclusion of the 14-day treatment period. Blood samples were obtained from the retro-orbital sinus, and creatinine concentrations were subsequently determined using an enzymatic assay method.

Histopathological Assessment of Renal Tubular Injury

Subsequent to the biochemical analysis, histopathological examination was performed to provide a more comprehensive evaluation of renal tubular damage. Following euthanasia, kidney tissues were harvested and fixed in neutral buffered formalin. The specimens were then processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). The severity of renal tubular injury was quantified based on key histopathological criteria, including tubular dilatation, loss of the brush border, epithelial cell thinning, and the formation of intraluminal casts. Microscopic analysis was conducted at 400× magnification across fifteen visual fields per sample, with evaluations performed independently by two blinded observers. Tubular damage was assessed using

a semiquantitative scoring system ranging from 0 to 4, where 0 represented normal histology, 1 indicated <25% injury, 2 denoted 25–50%, 3 signified 50–75%, and 4 represented >75% damage.

Literature Collection Strategy

A foundational element of this investigation involved the identification of authoritative and dependable literature. To this end, a systematic review of existing research was performed using targeted search terms, such as "celery extract," "nephroprotective effect," and "unilateral ureteral obstruction". To guarantee the scholarly rigor and pertinence of the gathered information, the researchers utilized prominent scientific databases, specifically ScienceDirect, PubMed Central, and Google Scholar.

Data Analysis and Summarizing

Statistical processing was performed utilizing IBM SPSS Statistics version 22.0. Prior to the primary analysis, the foundational assumptions of normality and homogeneity were verified using the Shapiro–Wilk and Levene's tests, respectively. Differences across the experimental groups were evaluated through a one-way ANOVA, supplemented by a post hoc least significant difference (LSD) test. The threshold for statistical significance was set at $p < 0.05$, and the study results were interpreted based on the findings of these comprehensive analyses.

RESULT

To assess the nephroprotective capacity of celery ethanol extract, 25 rats were divided into five cohorts (n=5): a sham control (Group A), a UUO negative control (Group B), and three treatment groups receiving dosages of 125, 250, and 500 mg/kgBW over 14 days,. The efficacy of these interventions was subsequently evaluated through serum creatinine measurement and histopathological assessment of renal tubular injury.

Difference in Mean Serum Creatinine Levels

Serum creatinine concentrations were analyzed at the conclusion of the treatment period to quantify renal functional integrity. Statistical analysis using one-way ANOVA demonstrated a significant disparity in mean serum creatinine levels between the sham control, the negative control, and the various extract-treated groups ($p<0.05$). While the induction of UUO in Group B led to the highest elevation of creatinine, the cohorts treated with celery extract (Groups C, D, and E) displayed a notable reduction in these levels compared to the negative control. Specifically, Group D (250 mg/kg) achieved the lowest creatinine levels among all experimental groups, suggesting it is the most effective concentration for preserving glomerular filtration. The comparative results of serum creatinine levels are presented in **Figure 1**.

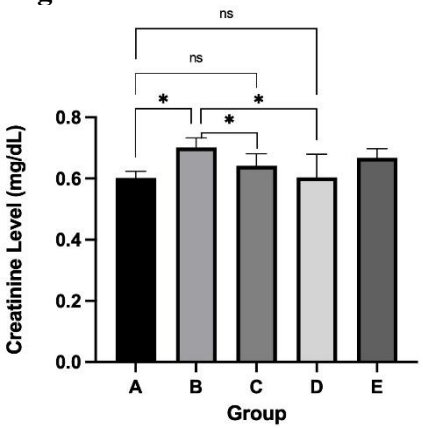

Figure 1. Comparison of serum creatinine levels among the study groups. Group A: sham control; Group B: negative control; Group C: celery ethanol extract 125 mg/kg body weight; Group D: celery ethanol extract 250 mg/kg body weight; Group E: celery ethanol extract 500 mg/kg body weight. ns: not significant; *: statistically significant.

Difference in Mean Renal Tubular Injury Score

To quantify the extent of renal architectural impairment following the treatment period, a histopathological assessment was conducted. Statistical analysis via one-way ANOVA revealed significant disparities in injury scores among the sham control, negative control, and cohorts receiving celery ethanol extract at dosages of 125, 250, and 500 mg/kgBW ($p < 0.05$). This evaluation utilized a semiquantitative scoring framework to examine key pathological markers, specifically tubular dilatation, brush border attrition, epithelial depletion, and the formation of intraluminal casts. Observations were standardized across fifteen visual fields per specimen and graded on a 0–4 severity scale, with scores expressed as mean values. Representative histopathological findings are presented in Figure 2, while comparisons of renal tubular injury scores are shown in Table 1 and Figure 3.

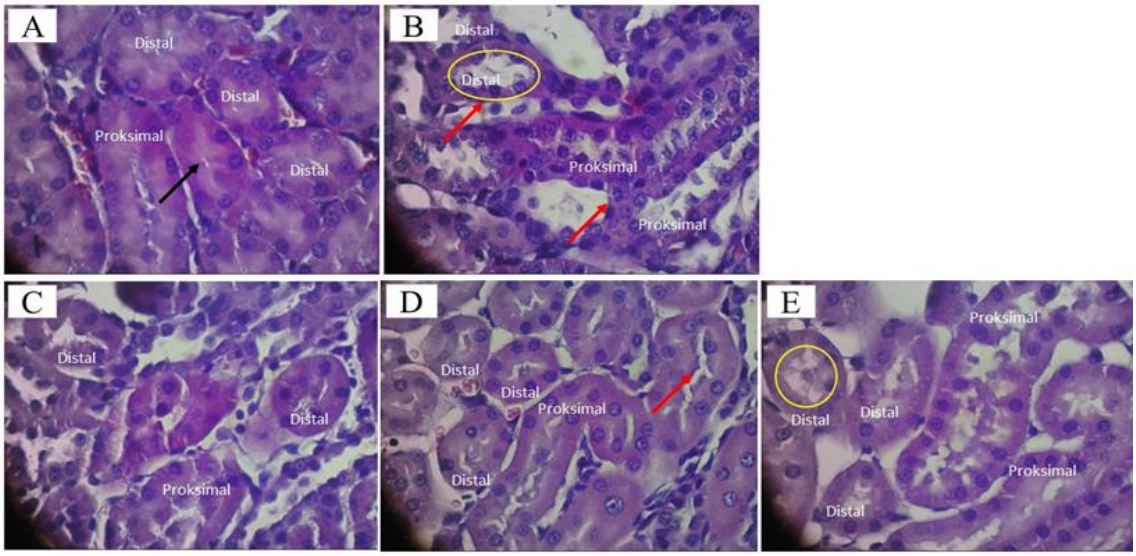

Figure 2. Representative kidney histology stained with hematoxylin and eosin (H&E) was examined under a light microscope at 400× magnification. Group A: sham control; Group B: negative control; Group C: UUO + 125 mg/kgBW celery ethanol extract; Group D: UUO + 250 mg/kgBW celery ethanol extract; Group E: UUO + 500 mg/kgBW celery ethanol extract. Black arrows indicate the brush border of proximal convoluted tubules; red arrows denote epithelial cell depletion; yellow circles highlight tubular dilatation.

While Group A (sham control) maintained normal renal histology with a baseline mean score of 0.21 ± 0.18, the cohorts subjected to unilateral ureteral obstruction (UUO) exhibited diverse levels of renal injury. The negative control (Group B) experienced the most acute structural insult, characterized by extensive tubular disruption and widespread epithelial loss, yielding a mean injury score of 2.96 ± 0.48. Conversely, among the extract-treated subjects, Group D (250 mg/kgBW) demonstrated the most effective attenuation of damage, with a mean score of 1.04 ± 0.36, which was significantly lower than that of the other treated groups. Subjects in the 125 mg/kgBW (Group C) and 500 mg/kgBW (Group E) cohorts displayed higher injury scores of 1.91 ± 0.42 and 1.90 ± 0.25, respectively, suggesting that the 250 mg/kgBW dosage provides the optimal therapeutic outcome within this experimental spectrum.

Table 1.
Average Kidney Tubular Injury Score

Group	N	Average Tubular Injury Score	SD
A: sham control	5	0,21	0,18
B: negative control	5	2,96	0,48
C: celery ethanol extract dose 125mg/kgBW	5	1,91	0,42
D: celery ethanol extract dose 250mg/kgBB	5	1,04	0,36
E: celery ethanol extract dose 500mg/kgBB	5	1,90	0,25

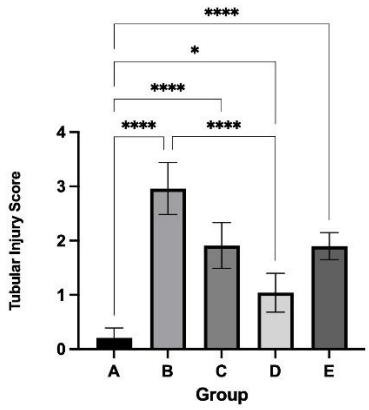

Figure 3. Comparison of renal tubular injury scores among post-treatment groups. Group A: sham control; Group B: negative control; Group C: celery ethanol extract (125 mg/kgBW); Group D: celery ethanol extract (250 mg/kgBW); Group E: celery ethanol extract (500 mg/kgBW). *: statistically significant.

DISCUSSION

Serum creatinine has long been recognized as a key biomarker for assessing renal function. Under normal conditions, serum creatinine levels in rats range from 0.4–0.8 mg/dL (Thammitiyagodage et al., 2020). In humans, normal serum creatinine levels are reported to range from 0.6–1.3 mg/dL. Creatinine, a waste product of muscle metabolism, is normally filtered by the kidneys and excreted in urine. When renal function is impaired, creatinine accumulates in the bloodstream, resulting in elevated serum creatinine levels. Therefore, increased serum creatinine is widely recognized as an important indicator of renal dysfunction and the severity of kidney injury (Wijaya et al., 2025). In line with this, the present study demonstrated markedly increased serum creatinine levels in the negative control group (Group B), indicating impaired renal function following UUO induction.

Notably, the effect of antioxidant compounds is highly dose-dependent. Previous studies have demonstrated that phenolic compounds possess potent antioxidant activity at low to moderate concentrations; however, at higher concentrations, they may undergo auto-oxidation and exhibit pro-oxidant properties, particularly in the presence of transition metal ions and molecular oxygen (Kruk et al., 2022). This shift from antioxidant to pro-oxidant activity may attenuate their protective effects and contribute to oxidative damage. Such a mechanism may explain the findings of the present study, in which serum creatinine levels increased in Group E (500 mg/kgBW), suggesting reduced renoprotective efficacy at higher doses.

Consistent with the biochemical findings, renal tubular injury represents a key pathological consequence of ureteral obstruction. Increased intratubular pressure and vasoconstriction lead to renal ischemia, which may progress to tissue necrosis and fibrosis (Widiani, 2020). Histopathological evaluation in this study was based on key features, including tubular dilatation, loss of brush border, epithelial thinning, and the presence of intraluminal casts. In agreement with the elevated serum creatinine levels, the negative control group (Group B) exhibited the most severe tubular injury (mean score: 2.96), which was significantly higher than that observed in the sham control (Group A; mean score: 0.21). Among the treatment groups, the lowest injury score was observed in Group D (250 mg/kgBW), with a mean value of 1.04, indicating a marked protective effect. In contrast, Groups C (125 mg/kgBW) and E (500 mg/kgBW) showed higher injury scores, suggesting less effective protection compared to the 250 mg/kgBW dose.

From a mechanistic perspective, the research indicates that the administration of celery ethanol extract at a dosage of 250 mg/kgBW successfully mitigates oxidative insult and restricts the progression of tubular degeneration. This nephroprotective outcome is likely attributed to flavonoid compounds present in celery, which possess antioxidant properties. Within the framework of the

unilateral ureteral obstruction (UUO) model, oxidative stress is generated by a physiological discrepancy between the overproduction of reactive oxygen species and the capacity of internal antioxidant systems. Flavonoids effectively counteract this imbalance by suppressing oxidative-mediated damage to renal tubular cells and the adjacent parenchyma, thereby maintaining the structural integrity and functional capacity of the kidneys (Agustiani et al., 2020). Furthermore, comparative statistical evaluations established a significant distinction in outcomes between the untreated negative control (Group B) and the cohort receiving the 250 mg/kgBW treatment (Group D). Consequently, the 14-day administration of 250 mg/kgBW celery ethanol extract following UUO induction was identified as the most efficacious therapeutic regimen among the evaluated concentrations.

CONCLUSION

This research demonstrates that celery ethanol extract significantly attenuates the elevation of serum creatinine levels and mitigates renal tubular injury within the unilateral ureteral obstruction (UUO) rat model. Among the concentrations evaluated, the 250 mg/kgBW dose was identified as the most efficacious therapeutic intervention for preventing the advancement of renal structural damage,. While these findings highlight the potential of celery as a candidate nephroprotective phytopharmaceutical, additional research is essential to fully characterize its safety profile through comprehensive toxicological evaluations and clinical trials.

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