

Antihypertensive Activity of Aqueous Celery (*Apium graveolens*) Leaf Extract at Different Dose Levels in a NaCl-Induced Hypertensive Murine Model

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Abstract:

Background: Hypertension is a major risk factor for cardiovascular disease, and there is increasing interest in herbal medicines as complementary antihypertensive therapies. Celery (*Apium graveolens*) has been reported to possess antihypertensive properties; however, evidence comparing the effects of different doses of celery leaf extract remains limited.

Objective: To evaluate the antihypertensive activity of aqueous celery (*Apium graveolens*) leaf extract at different dose levels in a NaCl-induced hypertensive murine model.

Methods: Twenty-four male mice were rendered hypertensive by administration of 2% NaCl for seven days and were then randomly assigned to four groups (n = 6 per group): a control group and three treatment groups receiving aqueous celery leaf extract at doses of 300, 400, and 500 mg/kg body weight/day for seven consecutive days. Blood pressure was measured at baseline (Day 0), after hypertension induction (Day 7), and after treatment (Day 14). Post-treatment systolic and diastolic blood pressure values were compared among groups using one-way ANOVA followed by Tukey's honestly significant difference (HSD) test.

Results: All treatment groups exhibited lower post-treatment systolic and diastolic blood pressure values than the control group. The 300 mg/kg body weight/day group showed the lowest post-treatment blood pressure values among the tested doses; however, no statistically significant differences were observed among the three treatment groups. Significant differences were identified between each treatment group and the control group ($p < 0.05$).

Conclusion: Aqueous celery (*Apium graveolens*) leaf extract demonstrated antihypertensive activity in NaCl-induced hypertensive mice. Within the tested dose range, increasing the dose above 300 mg/kg body weight/day did not provide additional antihypertensive benefit. Further studies evaluating a wider range of doses, longer treatment durations, and maintenance of the hypertensive stimulus are warranted to better characterize the antihypertensive potential of celery leaf extract.

Keywords: *Apium graveolens*; celery leaf extract; hypertension; antihypertensive activity; herbal medicine.

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INTRODUCTION

Hypertension continues to be a major global public health problem and is a significant risk factor for cardiovascular morbidity and mortality (Liu et al., 2025). While conventional antihypertensive medications are effective, long-term use is often associated with side effects and issues with treatment adherence. As a result, there is increasing interest in herbal therapies with potential antihypertensive effects and favorable safety profiles (Liu et al., 2025).

Medicinal plants comprise a source of diverse bioactive compounds that may lower blood pressure through multiple mechanisms, including vasodilation, antioxidative effects, diuresis, and modulation of neurohumoral factors (Anwar, Al Disi, & Eid, 2016). The standardization and evaluation of effective dose ranges are important for the development of safe and effective herbal antihypertensive agents. However, evidence comparing the antihypertensive effects of different doses of herbal extracts, including celery, remains limited.

Celery (*Apium graveolens*), a common vegetable and herbal remedy, has been historically used to manage hypertension in traditional medicine. Epidemiological and experimental studies have attributed antihypertensive properties to its biologically active constituents, including flavonoids such as apigenin and luteolin, and phthalides, particularly 3-*n*-butylphthalide (NBP) (Anwar, Al Disi, & Eid, 2016).

Clinical evidence also supports the blood pressure-lowering effects of celery preparations. In a randomized, triple-blind, placebo-controlled clinical trial, celery seed extract administered at approximately 1.34 g per day significantly reduced systolic and diastolic blood pressure in hypertensive patients compared with placebo (Farooq et al., 2022). Despite these findings, evidence comparing the antihypertensive effects of different doses of celery leaf extract remains limited, and it is still unclear whether increasing the dose provides additional therapeutic benefit.

Such information is important for supporting the development and standardization of herbal antihypertensive formulations (Anwar, Al Disi, & Eid, 2016).

Therefore, the present study aimed to evaluate the antihypertensive activity of aqueous celery (*Apium graveolens*) leaf extract at different dose levels in a NaCl-induced hypertensive murine model and to compare the antihypertensive effects among the tested doses.

MATERIALS AND METHODS

Materials

Fresh celery leaves (*Apium graveolens*) were obtained from a local agricultural supplier in Surabaya, Indonesia. Sodium chloride (NaCl) and all reagents used in this study were of analytical grade. Distilled water was used throughout the extraction and experimental procedures.

Preparation of Aqueous Celery Leaf Extract

Fresh celery leaves were washed thoroughly with running water to remove dirt and impurities, then air-dried at room temperature. The dried leaves were subsequently dried in an oven at 40–45 °C until a constant weight was achieved. The dried material was ground into a fine powder using a grinder.

Extraction was carried out using an aqueous decoction method. The powdered leaves were boiled in distilled water at a ratio of 1:10 (w/v) for 30 minutes. The mixture was allowed to cool to room temperature and then filtered using filter paper. The filtrate was concentrated by evaporation to obtain a crude aqueous extract. The extract was stored at 4 °C until further use.

Experimental Animals

Twenty-four male BALB/c mice aged 8–10 weeks with body weights ranging from 20 to 30 g were used in this study. The animals were housed under standard laboratory conditions (temperature 22–25 °C, 12 h light/dark cycle) with free access to standard pellet feed and drinking water. All animals were acclimatized for seven days prior to the experimental procedures.

Induction of Hypertension

Hypertension was induced by administering a 2% (w/v) NaCl solution as drinking water *ad libitum* for seven consecutive days. Baseline blood pressure measurements were recorded before NaCl administration to ensure that all animals were normotensive prior to induction.

Experimental Design and Treatment

This study employed a randomized controlled experimental design with repeated blood pressure measurements. Following hypertension induction and confirmation of elevated blood pressure on Day 7, the mice were randomly assigned into four groups (n = 6 per group):

- Control group (K): received 0.9% NaCl solution
- Treatment group P1: received aqueous celery leaf extract at a dose of 300 mg/kg body weight/day
- Treatment group P2: received aqueous celery leaf extract at a dose of 400 mg/kg body weight/day
- Treatment group P3: received aqueous celery leaf extract at a dose of 500 mg/kg body weight/day

All treatments were administered orally by gavage once daily for seven consecutive days (Day 8–Day 14). Blood pressure was measured at the end of the treatment period (Day 14) to evaluate the antihypertensive effects of the different doses of celery leaf extract.

Measurement of Blood Pressure

Systolic and diastolic blood pressures were measured using a non-invasive tail-cuff method. Measurements were performed at baseline (day 0), after hypertension induction (day 7), and after completion of the treatment period (day 14). Each measurement was repeated three times for each animal, and the average value was used for statistical analysis. Prior to data collection, the animals were acclimatized to the measurement procedure to reduce stress-related variability.

Ethical Considerations

All experimental procedures involving animals were conducted in accordance with institutional guidelines for laboratory animal care and use and were approved by the Ethics Committee of the Faculty of Medicine, Universitas Nahdlatul Ulama Surabaya, Indonesia (Approval No. 0422/EC/KEPK/UNUSA/2024).

Statistical Analysis

All data were expressed as mean $\pm$ standard deviation (SD). Baseline (Day 0) and post-induction (Day 7) blood pressure values were presented descriptively to demonstrate group homogeneity and successful hypertension induction. One-way analysis of variance (ANOVA) was performed to compare systolic and diastolic blood pressure values among the four experimental groups at the end of the treatment period (Day 14). Tukey's honestly significant difference (HSD) post hoc test was used for pairwise comparisons when the ANOVA results were significant. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS software.

RESULTS AND DISCUSSION

Results

All experimental animals completed the study without mortality or observable adverse effects throughout the experimental period. Baseline systolic and diastolic blood pressures were comparable among all groups, indicating homogeneous initial conditions prior to hypertension induction. Administration of 2% NaCl solution for seven consecutive days successfully induced hypertension in all experimental groups, as reflected by an increase in systolic blood pressure exceeding 140 mmHg and diastolic blood pressure exceeding 100 mmHg.

Following seven days of treatment, mice receiving aqueous celery (*Apium graveolens*) leaf extract showed a marked reduction in both systolic and diastolic blood pressures compared to the control group. The systolic and diastolic blood pressure values of all experimental groups at baseline, after hypertension induction, and after treatment are summarized in Table I. All treatment groups demonstrated lower blood pressure values at day 14 compared to the control group.

Among the treatment groups, the greatest reduction in blood pressure was observed in mice treated with 300 mg/kg body weight/day of celery leaf extract. Increasing the dose to 400 mg/kg and 500 mg/kg body weight/day did not result in further statistically significant reductions in either

systolic or diastolic blood pressure. One-way ANOVA showed significant differences in blood pressure among groups at the end of the treatment period ($p < 0.05$). Post hoc Tukey analysis confirmed that all treatment groups differed significantly from the control group, whereas no significant differences were observed among the treatment groups.

Table 1 Systolic and diastolic blood pressure of experimental groups

Group	Baseline (Day 0)	Post-induction (Day 7)	Post-treatment (Day 14)
Control	118/83 $\pm$ 4.1	146/101 $\pm$ 3.8	121/96 $\pm$ 4.5 ^a
P1	117/82 $\pm$ 3.9	145/100 $\pm$ 4.0	107/77 $\pm$ 3.7 ^b
P2	118/83 $\pm$ 4.2	146/101 $\pm$ 3.5	109/78 $\pm$ 4.1 ^b
P3	117/82 $\pm$ 4.0	147/102 $\pm$ 3.9	110/79 $\pm$ 3.8 ^b

Values are presented as mean $\pm$ SD ($n = 6$). Different superscript letters within the same column indicate statistically significant differences among groups (one-way ANOVA followed by Tukey's HSD test, $p < 0.05$). Groups sharing the same superscript letter are not significantly different.

DISCUSSION

The present study demonstrated that aqueous celery (*Apium graveolens*) leaf extract exerted significant antihypertensive effects in a NaCl-induced hypertensive murine model. Administration of the extract at all tested doses resulted in lower systolic and diastolic blood pressure values than those observed in the control group. Among the tested doses, the 300 mg/kg body weight/day group exhibited the lowest post-treatment systolic and diastolic blood pressure values. However, no statistically significant differences were observed among the three treatment groups, indicating that increasing the dose from 300 to 500 mg/kg body weight/day did not provide additional antihypertensive effects under the present experimental conditions.

From a pharmacological perspective, these findings suggest that increasing the dose beyond 300 mg/kg body weight/day did not produce additional antihypertensive effects within the tested dose range. This observation may reflect

receptor saturation, limited bioavailability of active constituents, or the activation of counter-regulatory physiological mechanisms, which have been described in phytopharmacological studies (Fardet & Rock, 2018; Heinrich et al., 2022). However, the present study was not designed to establish a complete dose-response relationship because only three dose levels were evaluated. Therefore, the findings should be interpreted as indicating that higher doses did not provide additional antihypertensive benefit within the tested dose range rather than demonstrating an optimal dose or a definitive dose-response relationship. These findings nevertheless highlight the importance of evaluating different dose levels during the development of herbal antihypertensive agents intended for long-term use (World Health Organization, 2018; Barnes et al., 2022).

The antihypertensive activity of celery leaf extract is likely mediated by the synergistic actions of its bioactive compounds. Flavonoids such as apigenin and luteolin have been reported to improve endothelial function by enhancing nitric oxide bioavailability, attenuate oxidative stress, and promote vascular smooth muscle relaxation, thereby reducing peripheral vascular resistance (Fardet & Rock, 2018; Malar et al., 2022; Harahap et al., 2024). In addition, apiin has demonstrated diuretic and vasorelaxant properties, contributing to reductions in blood volume and vascular tone (Moghadam et al., 2013). Furthermore, 3-*n*-butylphthalide, a characteristic phthalide compound found in celery, has been shown to inhibit calcium influx in vascular smooth muscle cells and modulate sympathetic nervous system activity, thereby reducing blood pressure (Li et al., 2019). A recent review further highlighted that the antihypertensive effects of celery are mediated through complementary antioxidant, anti-inflammatory, vasodilatory, and calcium channel-modulating mechanisms, supporting its potential as a multifunctional herbal antihypertensive agent (Alobaidi & Saleh, 2024).

The results of this study are consistent with previous experimental investigations reporting antihypertensive effects of celery extracts. Ahmed et al. (2021) demonstrated significant reductions in systolic and diastolic blood pressure in spontaneously hypertensive rats treated with standardized celery seed extract, attributing the

effect to vasorelaxant and angiotensin-converting enzyme inhibitory activities. Similarly, Widyawati et al. (2020) reported that aqueous celery leaf extract effectively lowered blood pressure in a salt-induced hypertensive rat model, supporting its potential as a natural antihypertensive agent. The present study extends these findings by directly comparing three dose levels of aqueous celery leaf extract in a NaCl-induced hypertensive murine model. Within the tested dose range, no additional antihypertensive benefit was observed with doses higher than 300 mg/kg body weight/day. This finding is in agreement with a recent systematic review and meta-analysis demonstrating that although celery preparations consistently reduce blood pressure, treatment efficacy may vary depending on the extract preparation, plant part, and dosage, emphasizing the importance of standardized formulations and well-designed dose evaluation studies (Liu et al., 2025).

A reduction in blood pressure was also observed in the control group following the treatment period, although post-treatment blood pressure values remained higher than those of all celery extract-treated groups. This observation suggests that spontaneous recovery may have occurred after the hypertension induction phase and indicates that the NaCl-induced hypertension model may not have been fully maintained throughout the experimental period. Consequently, part of the blood pressure reduction observed in the treatment groups may also have been influenced by spontaneous recovery rather than the celery extract alone. Nevertheless, the consistently lower post-treatment systolic and diastolic blood pressure values observed in all treatment groups compared with the control group suggest that aqueous celery leaf extract contributed additional antihypertensive effects beyond the spontaneous decline. Therefore, the antihypertensive activity of celery leaf extract should be interpreted relative to the control group rather than as an absolute treatment effect.

The present findings also have practical implications for the development of herbal antihypertensive formulations. Increasing the dose beyond the lowest tested dose did not improve antihypertensive efficacy, suggesting that dose escalation may not always provide additional therapeutic benefit. However, further studies

evaluating a broader range of doses are required to determine the minimum effective dose and to establish a complete dose-response relationship. Such investigations would facilitate phytochemical standardization, optimize formulation development, and strengthen the translation of promising preclinical findings into evidence-based herbal antihypertensive therapies (World Health Organization, 2018; Alobaidi & Saleh, 2024).

Several limitations should be acknowledged. The study employed a relatively short intervention period and focused solely on hemodynamic parameters without assessing biochemical markers such as nitric oxide levels, oxidative stress indicators, inflammatory mediators, or renin-angiotensin-aldosterone system activity. In addition, hypertension was induced only during the initial phase of the experiment and was not continuously maintained throughout the treatment period, which may have contributed to the reduction in blood pressure observed in the control group. Consequently, the magnitude of the antihypertensive effect attributable exclusively to celery leaf extract could not be determined with certainty. Furthermore, although the murine model provides valuable preclinical insight, extrapolation of these findings to human hypertension should be approached with caution. Future studies should maintain the hypertensive stimulus throughout the treatment period, incorporate mechanistic investigations, evaluate a wider range of dose levels, include positive control antihypertensive agents, and conduct long-term clinical studies to further validate the antihypertensive potential of celery leaf extract.

Despite these limitations, the present findings provide meaningful pharmacological evidence supporting the antihypertensive activity of aqueous celery leaf extract and contribute to the growing body of evidence regarding dose evaluation and the development of standardized herbal antihypertensive products.

CONCLUSION

The findings of this study demonstrate that aqueous celery (*Apium graveolens*) leaf extract possesses antihypertensive activity in a NaCl-induced hypertensive murine model. All tested doses reduced systolic and diastolic blood pressure compared with the control group, while no additional antihypertensive benefit was observed with doses higher than 300 mg/kg body weight/day under the present experimental conditions.

These findings suggest that increasing the dose within the tested range does not necessarily enhance the antihypertensive effect and highlight the importance of evaluating different dose levels during the development of herbal antihypertensive agents. However, because only three dose levels were investigated, the present study does not establish an optimal dose or a complete dose-response relationship.

Further studies involving a wider range of doses, maintenance of the hypertensive stimulus throughout the treatment period, mechanistic investigations, and long-term clinical evaluation are warranted to better characterize the antihypertensive potential of celery leaf extract and support its development as a standardized herbal antihypertensive candidate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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