

ORIGINAL ARTICLE

The effect of celery (*Apium graveolens* L) ethanol extract on the prevention of gastric ulcers in rats

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ARTICLE INFORMATION

Article history

Received March 31, 2023

Revised December 19, 2023

Accepted January 5, 2024

Keywords

gastric ulcer, ulcer lesion length, *Apium graveolens* L

ABSTRACT

Introduction: Gastric ulcer is an excoriation area of the stomach caused by the destruction of mucosal defense against the predominant factors. One of the efforts that should be made to reduce the incidence of gastric ulcers is a precautionary measure to use ethanol extract of celery (*Apium graveolens* L). Celery contains phenolic compounds, such as apigenin, which is an antioxidant. Antioxidants have the potential to act as agents of gastric mucosal protection against cell damage caused by excessive activation of free radicals (ROS).

Objectives: This study aimed to determine the effect of celery ethanol extract in preventing gastric ulcers by reducing ulcer lesion length. **Method:** Research method Posttest Only Randomized Controlled Group Design conducted on Wistar strain rats. The study involved 25 Wistar strain rats, which were randomly selected and divided into five groups. Experimental animals were divided into five groups: healthy, normal wound with induction indomethacin, and celery ethanol extract administered orally at 200 mg/kg, 300 mg/kg, and 400 mg/kg. Observations were made on the length of gastric ulcer lesions. The length of the gastric ulcer was measured using a vernier caliper and statistically analyzed using the One-Way ANOVA test. **Result:** The research showed that giving celery ethanol extract to treatment group 3 at a 300 mg/kg body weight dose showed the smallest Mean Length of Ulcer Lesions (1.33 ± 0.198). The results of the One-Way ANOVA test showed a significant difference between the control and treatment groups in reducing the length of gastric ulcer lesions ($p=0.000$). **Conclusion:** Based on these results, the researcher suggests comparing other parameters regarding the effect of celery ethanol extract on preventing gastric ulcers.

Journal of Nursing is a peer-reviewed journal published by the School of Nursing at the Faculty of Health Science, University of Muhammadiyah Malang (UMM), and affiliated with the Indonesia National Nurse Association (INNA) of Malang.

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1. Introduction

Gastric ulcer is an area of excoriation in the stomach caused by damage to the mucosal defense mechanism against predominant factors. This mechanism causes inflammation of the gastric mucous membrane. Gastric mucosal inflammation is associated with loss of mucosal integrity, gastric mucosal bleeding, decreased gastric mucosal antioxidant function, apoptosis of gastric mucosal cells, inhibition of cell renewal, and migration of gastric cells in epithelial damage (Zhang, Ning et al., 2023).

The prevalence of bleeding complications has increased over the past few years, especially at the age of 65 years and over. Patients with persistent bleeding are at high risk of death (Tarasconi et al., 2020). Gastric ulcer bleeding is a cause of gastric ulcer mortality with a percentage of more than 15% and has a high risk of recurrence (Seyoum et al., 2020). One of the causes of stomach ulcers is the use of NSAIDs (Nonsteroidal et al.) in the long term.

NSAID drugs are often used in clinical cases such as reducing pain and inflammation and as prevention and treatment of ischemic heart disease and antineoplastic agents (Da Costa et al., 2021). NSAIDs are used worldwide by more than 30 million people each year. More than 111 million prescriptions for NSAIDs are written each year, and 60% are sold freely in the USA (Tarasconi et al., 2020). The use of NSAID drugs significantly contributes to causing digestive tract disorders, such as being a factor in the emergence of ulcers and slowing ulcer healing (Zhang et al., 2022). According to the results of a study conducted in the Netherlands from 1996 to 2006, the incidence of gastric ulcers tended to be stable, with the number of gastric ulcer patients as many as 487 patients, the majority of whom were men (51%) (Groenen et al., 2009). The primary mechanism of NSAID drugs in causing stomach ulcers is in the form of inhibition of cyclooxygenase (COX) in the body.

Cyclooxygenase (COX) is divided into two isoforms, namely, COX-1 and COX-2. COX-1 is most abundant in gastric tissue and functions to maintain the integrity of the gastric mucosa, while COX-2 participates in the inflammatory process. NSAIDs, namely indomethacin, can cause gastric injury due to COX-1 inhibition, which causes prostaglandin deficiency in the gastric mucosa, resulting in gastric mucosal injury (Ju et al., 2022). The synthesis of prostaglandins functions as an inhibitor of excess gastric acid secretion in the gastric mucosa. The synthesis of prostaglandins is not the only pathogenic factor in ulcer development. Reactive Oxygen Species (ROS) also contribute to causing mucosal damage through the production of lipid peroxidation and oxidative damage (Eom et al., 2023). Other side effects of NSAIDs are marked by decreased blood flow to the gastric mucosa, decreased secretion of bicarbonate of mucus, impaired platelet aggregation, decreased epithelial cell regeneration, and increased leukocytes. This process has a clinical impact in the form of epigastric pain, nausea and vomiting, and loss of appetite (Kolawole & Kashfi, 2022).

Nausea is one of the nursing problems diagnosed in nursing (Hartati & Cahyaningsih, 2013). The role of the nurse in carrying out preventive measures using celery ethanol extract is needed to prevent a worse gastric ulcer prognosis and meet the basic needs of clients with gastric ulcers, namely the need for nutritional fulfillment (Xiao et al., 2021; Kurniawaty et al., 2020). One of the local manifestations that can be observed to determine the severity of gastric ulcers is the length of ulcer lesions on the gastric mucosa. One of the preventive measures that can be taken is administering ethanol extract of celery leaves orally (Musa et al., 2021).

Celery leaves (*Apium graveolens* L) is a plant that grows a lot in Indonesia. Celery leaves (*Apium graveolens* L) contain phenolic compounds such as apigenin, resveratrol, eriodictyol, 5,7-dihydroxychromone, and P-hydroxybenzoic acid (Taheri et al., 2022). The most significant content of these phenolic compounds is apigenin. Apigenin is an anti-inflammatory, antioxidant, antisecretion of stomach acid, and anticancer (Yoon et al., 2023). In previous studies, to identify anti-inflammatory activity in rat foot edema resulting from celery leaf extract, a significant dose as an anti-inflammatory was obtained, namely 300 mg/kg, while the duration of administration of celery ethanol extract as a preventive measure for gastric ulcers was for five days (Safira et al., 2021). Based on the function of apigenin, it is stated that celery ethanol extract can prevent gastric ulcers by reducing the length of ulcer lesions induced by indomethacin (Minaiyan et al., 2021). This study aimed to determine the effect of celery ethanol extract in preventing gastric ulcers by reducing ulcer lesion length.

2. Methods

The research design uses a genuine experimental laboratory with the Randomized Posttest Only Controlled Group Design method. The study involved 25 Wistar strain rats, which were randomly selected and divided into five groups. The research group was divided into five groups, namely the negative control group and healthy rats, and were not given any treatment. In the positive control group, the rats were only induced by indomethacin 30mg/kgBW given orally (sonde). Treatment groups 1, treatment 2, and Treatment 3 were each given celery ethanol extract at doses of 200 mg/kg, 300 mg/kg, and 400 mg/kg for five days orally (sonde), then induced by indomethacin on the sixth day (Syarifahnur et al., 2018).

2.1 Animals

This study used the Wistar strain white rat (*Rattus norvegicus*). The male rats were male with a body weight of 150-250 grams and 2-3 months of age. The number of research subjects used was 25 white rats, with five white rats in each group, and one additional rat was given to each group to anticipate the possibility of dropping out so that the total sample of Wistar strain white rats used in this study was 30 rats (Olivia & Agustini, 2019). All treatments for research subjects were approved by the Health Research Ethics Commission, Faculty of Medicine, Brawijaya University.

2.2 Extraction and Dosage

The celery leaves used in this study were *Apium graveolens* Linn. Materials for celery leaves were obtained from the East Java Provincial Health Office, UPT Materia Medica. 2 kg of celery leaves were washed and dried using an oven at 40°C. After the celery leaves are dry, please proceed with grinding to become a powder of 200 grams (Sapei et al., 2019). The following process was mixing celery leaf powder with 96% ethanol until the volume reached 1000 ml and allowed to stand for 24 hours until it evaporated. Then, the evaporation process is carried out by boiling the ethanol mixture with the active substance at a temperature of 70°C - 80°C; let the ethanol solution boil until it boils and then separate into the holding flask, wait \pm 1.5 hours to 2 hours until the ethanol solution stops dripping in the holding flask and only leaving the active substance, namely celery ethanol extract (B et al., 2023). The resulting extract is in the form of a paste.

In rats, the celery ethanol extract used in this study was 200 mg/kg, 300 mg/kg, and 400 mg/kg. Then, the celery ethanol extract was diluted with distilled water to change the dosage from liquid to liquid. The administration of celery ethanol extract to each rat is 2 ml per oral administration, where it is assumed that in 2 ml, there are 200 mg, 300 mg, and 400 mg of celery ethanol extract (Afifah et al., 2020).

2.3 Gastric Ulcer Prevention

After being acclimatized for seven days, the rats in the negative control group were still given food and drink according to laboratory standards and were not given any treatment until surgery, while the rats in the positive control group were only induced by indomethacin. Rats in treatment groups 1, 2, and 3 will each be given celery ethanol extract via oral (sonde) at doses of 200 mg/kg, 300 mg/kg, and 400 mg/kg for five days as a protective measure against the gastric mucosa (Guzmán-Gómez et al., 2018).

2.4 Gastric Ulcer Induction

The material used for gastric ulcer induction in this study was indomethacin at 30 mg/kg BW rats. The administration of indomethacin to each rat is 2 ml per oral administration, where it is assumed that 2 ml contains 30 mg of indomethacin. After five days of administration of celery ethanol extract, the rats were fasted for 18 hours but still given drinking water, then given indomethacin orally (sonde). This is done based on the indomethacin induction procedure so that the process of injury to the gastric mucosa can occur (Altuner et al., 2020).

2.5 Ulcer Lesion Length Measurement

Euthanasia of rats was carried out on the 14th day by giving chloroform per inhalation. Then, the rat's stomach was removed and dissected through the cardiac part through the greater curvature. The stomach is washed using PBS (phosphate-buffered saline) to remove impurities. Afterward, the stomach was placed on a styrofoam mat; a pin was inserted around the stomach organ and illuminated with a Visalux Energy Saver 8-watt Cool Daylight 360 LM 45 Lm/W lamp. Taking pictures of rat stomachs using a Canon 650D 18-megapixel camera at a distance of 30 cm. Identification of ulcer lesions, namely lesions in the gastric mucosa of varying sizes called erosions

(superficial lesions of the mucosa), have significant depth, with or without necrotic tissue in the center of the lesion. After the ulcer lesion was identified, the length of the ulcer lesion in the stomach was measured directly using a caliper, and the average length of the ulcer lesion was calculated in each rat's stomach (Susanto et al., 2021).

2.6 Data Analysis

The data were processed using the SPSS 20 for Windows program. They were analyzed using the One-Way ANOVA test and then continued with the post-hoc Tukey test with a confidence level of 95% ($\alpha=0.05$). The One-Way ANOVA test is used to determine whether there is a statistically significant difference between the means of three or more independent groups. The Tukey test was employed to conduct pairwise comparisons of treatment means after the variance test analysis.

3. Results and Discussion

Table 1 Data on Mean Length of Ulcer Lesions (Mean \pm SD)

Group	N	14 th day (mm) Mean \pm SD	P Value
Negative Control (N)	5	0 \pm 0	0.000
Positive Control (P0)	5	5.67 \pm 1.458	
Intervention 1 (P1)	5	3.13 \pm 1.973	
Intervention 2 (P2)	5	1.90 \pm 0.348	
Intervention 3 (P3)	5	1.33 \pm 0.198	

The research results on the effect of giving celery ethanol extract on preventing gastric ulcers by reducing the length of ulcer lesions in the stomach of rats induced by indomethacin were carried out by observing the rats macroscopically. The results of the study were observed after 12 hours of treatment. The average size of ulcer lesion length showed that the positive control group (P0) had the most extended ulcer lesion length (5.67mm), and the smallest size was in treatment group 3 (P3) (1.33mm). Data on the mean length of ulcer lesions can be seen in Table 1. The statistical test results for the length of ulcer lesions were analyzed using the One-way ANOVA test celery on decreasing the length of gastric ulcer lesions.

Table 2 Homogeneous subsets in statistical analysis of ulcer lesion length

Group	Subsets for $\alpha = 0,05$		
	1	2	3
Negative Control (N)	.00		
Intervention 3 (P3)	1.33	1.33	
Intervention 2 (P2)	1.90	1.90	
Intervention 1(P1)		3.13	
Positive Control (P0)			5.67
Sig.	.088	.119	1.000

The table shows that there are three subsets which show significant differences. Subset 1 was filled by the negative control group, treatment groups 2 and 3. This indicated that the average length of ulcer lesions in treatment groups 2 (P2) and 3 (P3) was statistically the same as normal gastric conditions. Likewise, subset two is filled with treatment groups P1, P2, and P3. This indicates that the treatment groups are not significantly different; that is, they have the same effectiveness in reducing the length of gastric ulcer lesions statistically with a significance value of each respectively ($p=0.432$), ($p=0.925$), ($p=0.119$). However, the positive control group was in

subset 3 (P3), which was different from the rest of the treatment group, indicating that indomethacin induction given to rats triggered injury to the gastric mucosa marked by a more significant length of ulcer lesions than the treatment group. From the data analysis, it can be concluded that administering 300 mg/kg BW celery ethanol extract orally is the best dose to prevent gastric ulcers by decreasing the length of ulcer lesions induced by indomethacin.

In Figure A, it appears that there is no gastric ulcer; this indicates that under normal conditions, the rat stomach does not form gastric ulcers, and the smooth membrane that protects the surface of the stomach is still visible. From Figure B, it can be seen that there is a gastric ulcer in a linear form (straight line); this indicates that indomethacin induction can cause ulcers in the stomach of rats. In Figures C, D, and E, the administration of celery ethanol extract at doses of 200 mg, 300 mg, and 400 mg, respectively, shows a minor stomach ulcer compared to the positive control group.

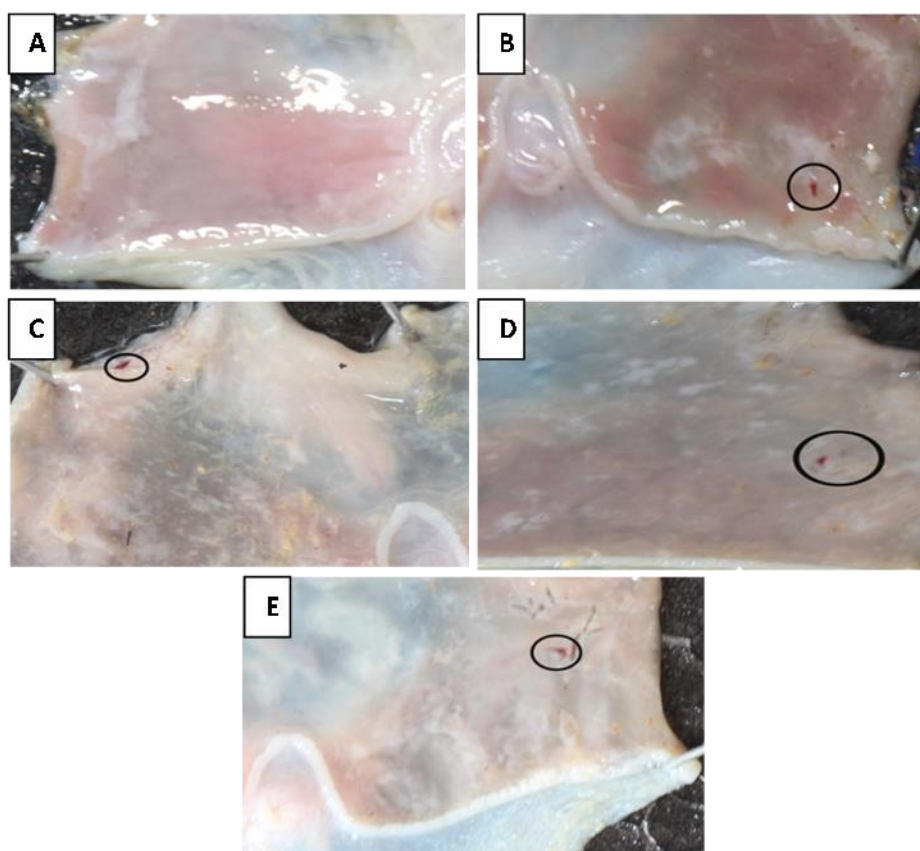


Figure 1. Macroscopically, the condition of the rat gastric on day 14 in the negative control group (A), positive control group (B), treatment group 1 (C), treatment group 2 (D), and treatment group 3 (E).

The study was conducted to analyze the differences in the length of gastric ulcer lesions in the control group and treatment groups P1, P2, and P3, which were respectively given celery ethanol extract orally at doses of 200 mg/kg, 300 mg/kg, and 400 mg/kg for five days before indomethacin induction as a preventive measure. The results of the one-way ANOVA test showed a significant difference between the control and treatment groups in terms of reducing the length of gastric ulcer lesions. Administration of celery ethanol extract in treatment groups P1, P2, and P3 showed a decrease in the mean length of gastric ulcer lesions with respective values (3.13 ± 1.973), (1.90 ± 0.348), and (1.33 ± 0.198). The results of the above study showed a significant

difference in the length of gastric ulcer lesions between rats in the control and treatment groups; this proved the contribution of celery ethanol extract to preventing gastric ulcers.

The results revealed that rats administered with indomethacin induction developed gastric ulcers. Previous research on experimental animals has demonstrated that indomethacin induction can lead to gastric ulcers. This mechanism is believed to inhibit the cyclooxygenase (COX) enzyme, which plays a crucial role in prostaglandin synthesis and biosynthesis (Fang et al., 2019). Generally, nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin have been linked to an increased risk of severe gastrointestinal disorders, including bleeding, ulceration, and perforation (Watanabe et al., 2020).

The cyclooxygenase enzyme (COX) is a membrane-bound bifunctional enzyme responsible for producing prostanoids such as prostaglandins and endoperoxides. COX is classified as an isoenzyme with two main isoforms: COX-1 and COX-2. COX-1 is constitutively expressed to maintain normal physiology and homeostasis, whereas COX-2 is induced in cells during inflammation by various factors such as cytokines, endotoxins, and growth factors (Jang et al., 2020). COX plays a critical role in prostaglandin formation through two key stages: cyclooxygenation and peroxidation. The cyclooxygenation stage involves cyclization and adding two oxygen molecules to arachidonic acid to form prostaglandin G₂ (PGG₂). Subsequently, the peroxidation stage entails the reduction of PGG₂ to endoperoxide compounds (Suñer-Rubio et al., 2019).

The study results revealed a significant difference in the length of gastric ulcer lesions observed between the control group and the treatment group receiving oral celery ethanol extract. Experimental animals in the treatment groups (P1, P2, and P3) showed a decrease in the mean length of gastric ulcer lesions compared to the positive control group. Prevention of gastric ulcers through indicators of decreasing the length of ulcer lesions is related to the presence of flavonoids in celery leaves, and based on the phytochemical analysis of the methanol extract of celery leaves, indicated that the most significant content of flavonoids and phenolic compounds was apigenin, as much as 202 mg/1000gr (Ginwala et al., 2019). These phenolic compounds include luteolin and chrysoeriol 7-glucosides, which contain 48mg/1000gr and 27mg/1000gr, respectively. In addition, celery also contains furanocoumarin, psoralen, bergapten, xanthotoxin, and isopimpinellin in varying amounts ranging from 12-50mg/1000gr. These ingredients function as antioxidants in the body. The antioxidant effect has the potential as a protective agent against cell damage caused by excess free radical activation (ROS) (Vona et al., 2021). The gastroprotective effect occurs through several mechanisms: increasing blood flow in the stomach, stimulating the synthesis of mucous substances in the gastric mucosa, and increasing the effects of prostaglandins (Zhang, Liu, et al., 2023).

The antioxidant effect associated with antiulcerogenic activity arises by strengthening the mucosal barrier, the first defense against endogenous and exogenous ulcerogenic agents (Davoudi-Kiakalayeh et al., 2017). Previous studies have stated that flavonoids are associated with antiulcer activity and play an essential role in the mechanism of gastroprotection. The content of flavonoids found in celery leaves can protect the mucosa by preventing the formation of lesions by necrotic agents. Flavonoids contain antioxidants that increase the mucosal defense system by stimulating gastric mucus secretion, and flavonoids can also be direct "scavengers" of ROS (Kim et al., 2020). In addition, the protective effect produced by antioxidants affects the reduction of the formation of lesions in the mucosa by inhibiting neutrophil infiltration of gastric tissue. Neutrophils induce the formation of lipid peroxidation through the production of superoxide anions (Chniguir et al., 2019). Neutrophils are the largest source of ROS production, including superoxide, hydrogen peroxide, and myeloperoxidase. Some ROS agents are cytotoxic and can cause tissue damage (Tanabe et al., 2022). Continuous accumulation of neutrophils can cause abnormalities in the microcirculatory associated with decreased blood flow to the stomach (Fournier & Parkos, 2012). Based on the study's results, administering ethanol extract of celery-containing antioxidants can protect the gastric mucosa against indomethacin induction. This

protection has been proven in this study, which states that the three treatment groups significantly reduce the length of gastric ulcer lesions.

Several studies have investigated the potential of plant materials in preventing gastric ulcers, yielding promising results. For instance, research on male white rats of the Wistar strain demonstrated that administering honey at various concentrations could influence the gastric histopathological picture induced by indomethacin (Ranneh et al., 2021). The study found that the group that administered honey at specific concentrations exhibited lower degrees of gastritis and peptic ulcers than the control group. Another study focused on evaluating the acute toxicity of ethanol extract of dewa leaves in the stomachs of mice. The findings indicated that the ulcer index did not increase linearly with increasing dose (Evi Sovia et al., 2023). This observation suggests that the compounds present in medicinal plants may not exhibit a linear dose-response relationship.

Additionally, systematic studies have been undertaken to evaluate the antiulcerative activity of various herbal plants and their potential as cultivated crops. Research outcomes have highlighted the gastroprotective potential of several herbal plants, including *Moringa oleifera* and *Allium fistulosum* (Ijioma et al., 2018; Ullah et al., 2020). While these research findings demonstrate the potential of plant materials in preventing gastric ulcers, further studies are necessary to assess their effectiveness and safety for human use. Continued research efforts will contribute to validating these plant-based interventions and their integration into clinical practice for managing gastric ulceration.

The histopathological evaluation of the stomach further confirmed the results of the in vivo experiments. Upon examination, it was observed that ethanol treatment resulted in hemorrhagic necrosis of the gastric mucosa in mice. However, initial treatment with celery extract did not lead to ulceration or bleeding in the gastric antrum. These histological findings align with the pharmacological and biochemical parameters assessed in the study.

In summary, the findings of this research suggest that the ethanol extract of *Apium Graveolens* possesses gastroprotective activity. This was evidenced by its significant inhibition of ulcer formation induced by various experimental models and its ability to reduce basal gastric acid secretion. The anti-gastric ulcer properties of celery extract are likely attributed to its antioxidant properties, which contribute to the reduction of lipid peroxidation and enhancement of the gastric mucus layer. Based on these observations, celery extract, owing to its antioxidant effects, may hold potential for the prevention of gastric disorders. Further research and clinical studies are warranted to explore celery extract's therapeutic implications in managing and preventing gastric ulcers and related conditions.

4. Conclusion

Oral administration of celery ethanol extract can prevent gastric ulcers by reducing the length of ulcer lesions in indomethacin-induced white Wistar rats. Effective administration of celery ethanol extract is at a dose of 300 mg/weight. Researchers suggest conducting further research by comparing parameters related to the mechanism of gastric ulcer occurrence. Indeed, while celery juice may offer potential benefits for individuals with gastritis, it is essential to approach any dietary or herbal intervention with caution, especially if you have underlying health conditions or are taking medications. Consulting with a healthcare professional, such as a doctor or herbalist, before incorporating celery juice or any alternative treatments into your routine is advisable.

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