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ORIGINAL ARTICLE

Hepatoprotective effects of celery in diethylene glycol induced toxicity in rats

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ABSTRACT

BACKGROUND
Diethylene glycol (DEG) is a contaminant in pharmaceutical solvents and potentially induces hepatotoxicity. Celery is hepatoprotective due to its antioxidant properties. The objective of this study was to evaluate the hepatoprotective effects of celery on DEG-induced liver injury in rats.

METHODS
An experimental laboratory study was conducted involving 25 male Wistar rats weighing 200 grams. They were randomized into five groups (5 rats in each group). Group A served as the control group, while Group B received oral administration of DEG at a dose of 3 g/kg BW twice daily for three days, following six days of food and water administration. The other three groups received DEG at 3 g/kg BW following six days of celery extract once daily administration of 100 mg/kg BW (C), 200 mg/kg BW (D), and 400 mg/kg BW (E). After 14 days, all rats were sacrificed. Observations were conducted macroscopically and microscopically using H&E staining. Liver damage was scored, Kruskal-Wallis followed by the Mann-Whitney was used to analyze the data.

RESULTS
Macroscopic and microscopic examinations of the liver tissue in the celery groups revealed normal histological architecture with a significant reduction in liver damage. The ethanol extract of celery demonstrated hepatoprotective effects, as evidenced by a statistically significant reduction ($p<0.05$) in the activation of Kupffer cells, sinusoidal dilation, hepatocyte degeneration, and necrosis.

CONCLUSION
Celery has a protective effect against DEG-induced liver damage in rats based on the reduction in Kupffer cell activation, sinusoidal dilation, hepatocyte degeneration, and necrosis.

Keywords: Celery, hepato-protector, diethylene glycol, rats

INTRODUCTION

The liver serves as the principal organ for detoxification within the human body, playing a critical role in the metabolism of pharmaceuticals and toxic substances. The majority of drugs and toxins can be eliminated from the body through biotransformation processes that occur in the liver. However, the liver is susceptible to damage from a variety of pharmaceutical agents and environmental chemicals. Certain medications and their active metabolites have the potential to induce hepatic injury, resulting in conditions such as drug- or toxin-induced hepatitis.[1,2] The histopathological architecture of the liver constitutes one of the evaluative parameters for assessing the toxicological impact of various compounds.[3] A notable substance associated with hepatic injury is diethylene glycol (DEG), a clear and odorless solvent that can occasionally occur as a toxic contaminant in pharmaceutical preparations. The threshold for adverse effects is exceeded when an intake of 0.5 mg per kilogram of body weight is maintained on a daily basis.[4] The underlying cause of this toxicity may be attributed to the formation of a toxic metabolite, diglycolic acid (DGA). In rat models, alcohol dehydrogenase (ADH) in the liver metabolizes DEG into the intermediate compound 2-hydroxyethoxyacetaldehyde (HEAA) and DGA, which subsequently leads to metabolic acidosis and resultant cellular injury in hepatocytes and the kidneys.[4,5]

Recently, herbals have gained popularity as complementary treatments for inflammation and oxidative stress associated with free radicals and toxic exposure, primarily due to their low toxicity profiles.[6] One of the notable medicinal plants is celery (*Apium graveolens*), a green plant recognized for its antioxidant and anti-inflammatory properties. This plant encompasses a variety of bioactive compounds, including tannins, saponins, apigenin, luteolin, and kaempferol, which serve as antioxidants.[7] Its therapeutic effects encompass benefits for hypertension, anti-inflammatory actions, diuretic effects, and the reduction of liver fat accumulation.[8] Previous studies have indicated that celery extract may confer protective effects against liver damage induced by toxic agents.[9] Specifically, celery extract has been shown to reduce inflammation and enhance total antioxidant capacity (TAC) and glutathione (GSH) levels.[9] Notably, celery has demonstrated hepatoprotective effects in instances of acetaminophen-induced toxicity. Emad et al.[9] reported that pretreatment with a low dose of celery (100 mg/kg body weight) significantly decreased liver enzyme levels (AST and ALT) and inflammatory markers (TNF-α and IL-1β) in rats exposed to acetaminophen. The antioxidant effects of celery on inflammation and arthritis have been investigated in a study by Sukketsiri et al.[10] They employed complete Freund's adjuvant in their animal model, while we used diethylene glycol in our study. Celery at dosages of 250–500 mg/kg BW have demonstrated a beneficial effect against liver oxidative stress by lowering the production of liver free radicals and raising the activity of liver antioxidant enzymes.

The hepatoprotective properties of celery were investigated in two earlier studies and our results confirm them. In the two previous investigations, complete Freund's adjuvant[10] and paracetamol[9] were utilized, respectively. In ours, diethylene glycol was used. Damage to the liver might result from all of the three aforenamed chemicals. According to the findings of our study and earlier research, celery may have hepatoprotective effects. The use of diethylene glycol differentiates our study from previous studies. Our choice of diethylene glycol was based on the fatalities caused by diethylene glycol poisoning in syrup preparations that occurred in Indonesia in 2022.[11] Our study aimed to evaluate the hepatoprotective effects of celery on DEG-induced liver toxicity by analyzing histopathological features in rat liver tissue.

METHODS

Research design

A post-test only laboratory experimental study with control, conducted from July – December 2023 in the Pharmacology and Clinical Pharmacy Laboratory, Pharmacy Department, Faculty of Health Sciences, Jenderal Soedirman University and the Anatomical Pathology Laboratory, Faculty of Medicine, Gadjah Mada University.

Materials

The tools used in this study included a vacuum pump, an analytical balance (Radwag AS 220.R2, Poland), filter paper, a rotary evaporator (Buchi, Rotavapor R-3, Switzerland), glassware, a probe, and syringes for oral administration of turmeric ethanol extract and DEG.

For histological preparation, the following tools were used: coverglasses, microscope glass slides, tissue embedding cassettes, a rotatory microtome (Shandon AS 325, United Kingdom), styrofoam, histoplast, a paraffin dispenser, and a light microscope (CX23, China). The materials for histology slide preparation included 10% formalin solution for fixation, alcohol, xylene, hematoxylin-eosin (HE) stain (Mayer's Hematoxylin Solution, USA), paraffin media, 0.9% NaCl, and 10% buffered neutral formalin (BNF).

Celery powder was obtained from and has been authenticated by the Testing Laboratory-Traditional Medicine Functional Service Unit, Tawangmangu, Central Java. Other materials included DEG (Merck KGaA, Germany), 96% ethanol (Merck ETHANOL 96% Reag. Ph. Eur., Germany), Tween 80, and standard rat feed.

Experimental animals

Male Wistar rats (2 months old, weighing 200 grams) were obtained from the Faculty of Pharmacy, Muhammadiyah Purwokerto University, Purwokerto, Indonesia. The rats were acclimatized for five days, were given standard pelleted feed and water ad libitum, and maintained on a 12:12-hour light-dark cycle. The sample size for this study was determined based on the number of experimental repetitions, calculated using Federer's formula: $(k-1)(n-1) \geq 15$, where n = number of samples; k = number of treatments.

Based on these calculations, each treatment group required a minimum of 5 repetitions, leading to a total of 25 experimental animals for the five groups. To account for potential unforeseen circumstances, one additional animal was included per group, resulting in a total of 30 Wistar rats.

A post-test only control group design was used for this experimental study. After the acclimatization period, the rats were divided into five groups, with five rats per group. Group A (control group) received only food and water. Group B received DEG orally at 3 g/kg BW twice daily for three days, following six days of food and water administration. Groups C, D, and E were treated with DEG (3 g/kg BW) and following six days of celery extract administration at doses of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW, respectively.[12] The celery extract, dissolved in Tween 80, was administered orally twice daily for six days. On day 14, all rats were sacrificed, and histopathological damage to the kidneys and liver was assessed using hematoxylin-eosin (HE) staining.

Preparation of celery extract

A total of 1000 grams of celery powder was extracted using 96% ethanol in a ratio of 1:5 for the first maceration and 1:4 for the 3x24 hours. Filtration was performed every 24 hours, and the filtrate was concentrated using a rotary evaporator to obtain a solvent-free, thick extract.

Hematoxylin-Eosin (H&E) staining

On day 14, all rats were sacrificed via cervical dislocation. The kidneys and livers were removed and fixed in 10% buffered formalin. After fixation, tissue samples (3-5 cm slices) were embedded in paraffin, sectioned, and stained with H&E for histological examination. The staining procedure was performed by the Anatomical Pathology Laboratory, Faculty of Medicine, Gadjah Mada University. Two trained researchers, under the guidance a pathologist, independently examined the specimens using a binocular microscope (Optilab microscope digital camera system) at 400x magnification.

Grading of liver damage

Liver damage was scored based on the percentage of injury across four parameters: Kupffer cell activation, sinusoidal dilation, hepatocyte degeneration, and necrosis. The scoring criteria were as follows: 0 for normal, 1 for damage <30%, 2 for damage 30-50%, and 3 for damage >50%.[13] One hundred cells were examined in order to determine the scoring system. If there is no damage, the score is zero; if there is less than thirty damaged cells, the score is one. If 30–50 cells suffer damage, the score is 2, and if more than 50 cells are damaged, the score is 3. For every organ preparation sample, the results were acquired from five fields of view at a 400x magnification.

Statistical analysis

Liver damage scores were statistically analyzed. The Shapiro-Wilk test was used to assess normality of data distribution. We analyzed four sets of data, of which the necrosis data, was not normally distributed. Therefore, we performed non-parametric analysis using the Kruskal-Wallis test, followed by the Mann-Whitney U test. This analysis evaluated statistical differences, with a p-value <0.05 being considered significant.

Ethical clearance

The animal experiments were approved by the Ethics committee of the Faculty of Health Sciences, Jenderal Soedirman University, under ethical approval number 1108/EC/KEPK/V2023.

RESULTS

The liver's color, size, and consistency can all be examined at a macroscopic level. Figure 1 illustrates that the livers of groups B and C of rats exhibited a color change to pale brown. Table 1 shows the macroscopic appearance of each group of Wistar rat livers. The liver color in the normal group (A) was reddish-brown. Compared to groups B and C, the liver color changed to pale brown. The liver color in groups D and E was reddish-brown, the same as that of group A. The four groups are all of the same size and consistency—four centimeters and firm. Histopathological observations of the liver (Figure 2) identified various forms of tissue damage. Hepatocyte degeneration, necrosis, sinusoidal dilatation, and Kupffer cell activation are some of the indicators of liver injury that are observed. Table 2 shows the histopathological damage score based on scoring. The Shapiro-Wilk test for normality indicated that the data was not fitted to the normal distribution curve ($p<0.05$). In light of the results, it was reasonable to perform non parametric tests, and Kruskal-Wallis test revealed such differences between the groups. The Mann Whitney test was then carried out to investigate whether pairwise differences exist.

Data in Table 2 shows that Group B (DEG 3g) had significant the highest average Kupffer cell activation, followed in descending order by Groups E (DEG 3g + Celery 400 mg/kb BW), A (Normal), C (DEG 3 g + Celery 100 mg/kg BW), and D (DEG 3g + Celery 200 mg/kg BW) ($p <0.05$). Similarly, the greatest average sinusoidal dilation was found in Group B, with the lowest averages in Groups A, D, C, and E, respectively. Hepatocyte degeneration was most prominent in Group B, with the lowest averages observed in Groups D, C, E, and A. Finally, necrosis was most prevalent in Group B, with no signs of necrosis detected in any of the other groups.

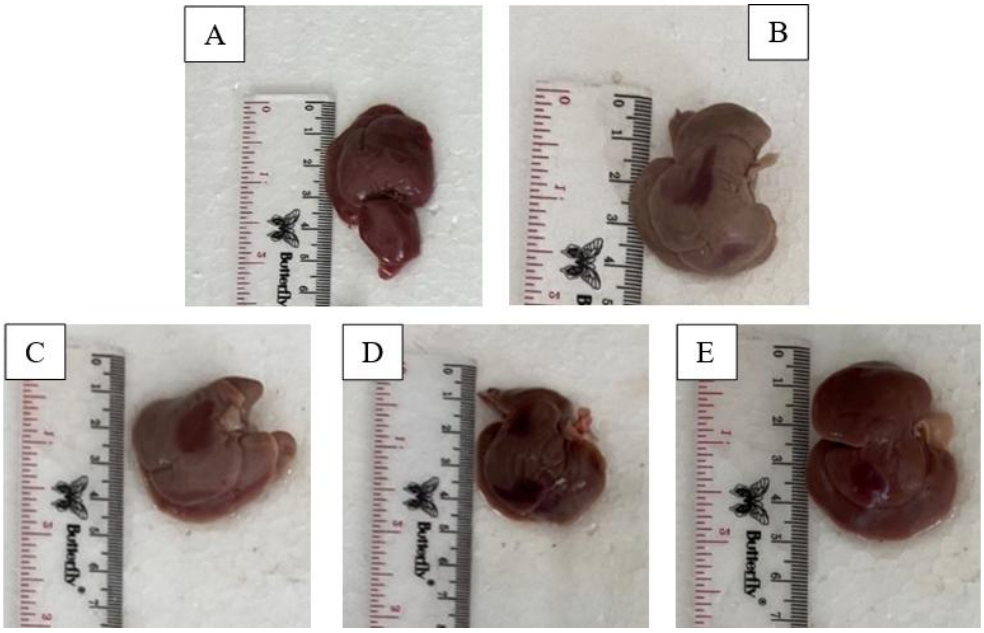

Figure 1. Macroscopic observations of rat livers

Table 1. Results of macroscopic observations of rat liver organs

Treatment Group	Liver Morphology		
	Color	Size	Consistency
A (Normal)	Reddish-brown	4 cm	Firm
B (DEG 3 grams)	Pale brown	4 cm	Firm
C (Celery 100 mg/kg BW + DEG 3 grams)	Pale brown	4 cm	Firm
D (Celery 200 mg/kg BW + DEG 3 grams)	Reddish-brown	4 cm	Firm
E (Celery 400 mg/kg BW + DEG 3 grams)	Reddish-brown	4 cm	Firm

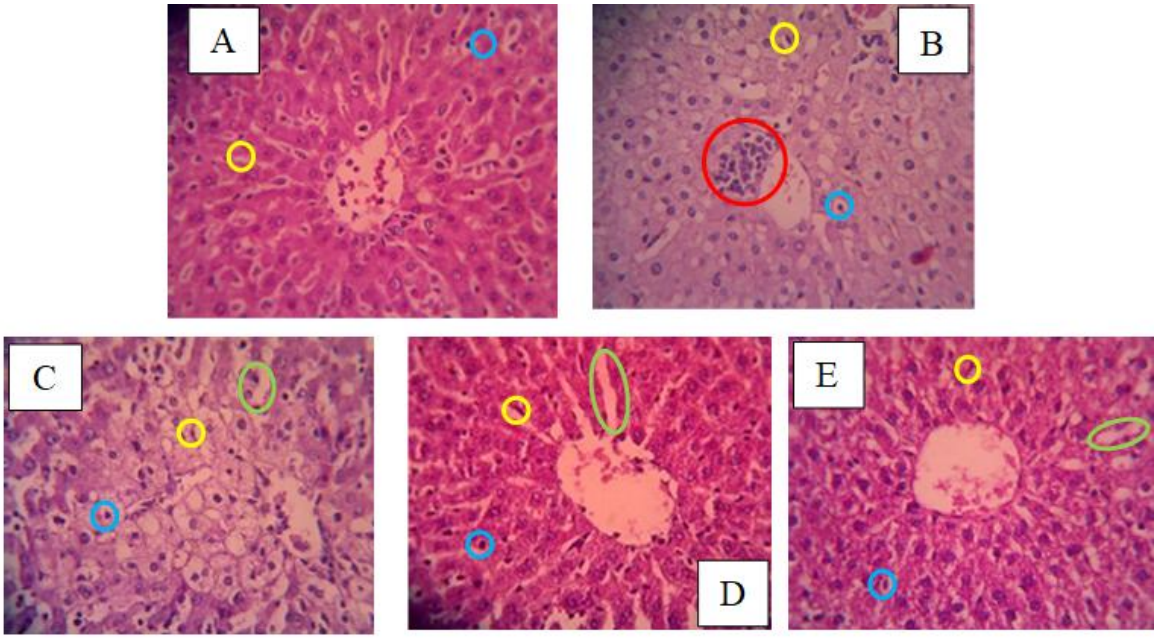

Figure 2. Histological evaluation on the liver of control and experimental groups

Note: (A) normal; (B) DEG 3 g; (C) Celery 100 mg/kg BW + DEG 3 g; (D) Celery 200 mg/kg BW + DEG 3 g; (E) Celery 400 mg/kg BW + DEG 3 g; (○): Kupffer cell activation; (○): Hepatocyte degeneration; (○): Sinusoidal dilatation; (○): Necrosis. Hematoxylin-Eosin stain. Magnification 400x.

Table 2. Histopathological liver damage based on scoring

	Treatment groups					
	Normal (A)	**DEG 3 g (B)**	**DEG 3 g +Celery 100 mg/kg BW (C)**	**DEG 3 g +Celery 200 mg/kg BW (D)**	**DEG 3 g +Celery 400 mg/kg BW (E)**	**p value**
Kupffer cell activation	0.44 ± 0.07	1.40 ± 0.06^{a}	1.00 ± 0.06^{b}	0.60 ± 0.06	0.68 ± 0.13	<0.05$^{@}$
Sinusoidal dilatation	0.84 ± 0.11	2.60 ± 0.14^{a}	1.92 ± 0.04^{a}	1.32 ± 0.04^{b}	1.44 ± 0.07^{b}	<0.05 $^{@}$
Hepatocyte degeneration	0.16 ± 0.04	1.04 ± 0.07^{a}	0.68 ± 0.04^{b}	0.40 ± 0.06^{b}	0.24 ± 0.07	<0.05 $^{@}$
Liver necrosis	0.00 ± 0.00	0.88 ± 0.04^{a}	0.48 ± 0.08^{b}	0.24 ± 0.07^{b}	0.12 ± 0.08	<0.05$^{@}$

Note : DEG : diethylene glycol; * : p<0.05;$^{@}$ indicate Kruskal-Wallis test followed by Man Whytney test; Means with differing superscript within rows were significantly different at the p<0.05

DISCUSSION

A normal liver exhibits a reddish-brown color, attributable to the influx of blood into the organ.[14] The livers of the DEG and 100 mg/kg BW extract groups exhibited a color change to pale brown, suggesting liver damage, which disrupts the normal blood flow and results in the paler appearance of these livers.[15] Such damage is associated with the rapid release of free fatty acids from the larger visceral fat mass (the adipose tissue surrounding the internal organs).[16] Kupffer cell activation was marked by flat, oval-shaped, purple-stained structures around the sinusoidal wall. Hepatocyte degeneration appeared as dark purple, round structures near the sinusoidal wall. Sinusoidal dilation was identified by increased spaces between the sinusoids, showing as empty spaces, while necrosis was observed in hepatocytes lacking visible nuclei.[17]

This study demonstrated that celery leaf ethanol extract exerts a hepatoprotective effect on Wistar rats induced with diethylene glycol. The celery extract at doses of 200 and 400 mg/kg BW showed better hepatoprotective effects compared to the 100 mg/kg BW dose. The Mann-Whitney

test results between the 200 mg/kg BW and 400 mg/kg BW groups indicated a numerical but statistically non-significant difference, suggesting minimal but non-significant variation in effect based on dose. This slight difference in effect could potentially result from the relatively short duration of treatment, which may necessitate a longer treatment period for more pronounced effects.[18]

The Mann Whitney test for the 200 mg/kg BW celery dose yielded significant results when compared to the negative control group, aligning with findings from Susilo et al.[19] This prior study similarly identified the hepatoprotective benefits of celery extract at 200 mg/kg BW, highlighting that flavonoids effectively serve as antioxidants at this dose. The efficacy of flavonoids in a hepatoprotective role is notably dose-dependent, contributing optimally at specific concentrations.

Based on the results, the healthy control group (Group A) showed a high number of normal hepatocytes, though some minor damages were identified, such as Kupffer cell activation, sinusoidal dilation, and hepatocyte degeneration; however, no necrosis was observed. Minor cellular damage in the normal (healthy control) group is considered a typical part of the body's physiological mechanisms. Nevertheless, immune suppression or stress factors in rats can trigger further cellular damage.[20]

In the negative control group (Group B), numerous indicators of hepatocyte damage were observed, including necrosis, sinusoidal dilation, Kupffer cell activation, and cellular degeneration. This damage is attributed to the accumulation of the DEG metabolite, specifically diglycolic acid (DGA), in the liver, which generates highly reactive compounds known as reactive oxygen species (ROS) that lead to lipid peroxidation.[21] Lipid peroxides damage the lipid membrane, increasing cell permeability and subsequently causing cellular swelling.[22] Reactive oxidative stress (ROS) released by damaged parenchymal cells can activate Kupffer cells, signifying the liver's regenerative response.[23]

Hepatocyte degeneration serves as an important indicator of the onset of cellular damage induced by toxic agents. This degeneration may occur when cells undergo alterations in their normal structure due to both intracellular and extracellular influences, which are often characterized by metabolic disorders.[1,24] Damaged hepatocytes exhibit irregular morphologies, resulting in a disorganized arrangement of hepatocytes within the lobules. Consequently, the sinusoids that border the hepatocytes experience dilation. This sinusoidal dilation may also be attributed to elevated levels of toxins in the bloodstream that traverse the sinusoids toward the central vein.[25] The anatomical configuration of the sinusoids permits direct exposure to toxins released from hepatocytes, as the sinusoids are comprised of endothelial cells. The interaction between sinusoids and hepatocytes is facilitated by subendothelial gaps containing microvilli that extend from the hepatocytes. This structural arrangement promotes close contact between the hepatocyte surface and the sinusoidal lumen, thereby enhancing the exchange of various compounds, including toxins.[26]

In the negative control, numerous cells exhibited signs of inflammation; this phenomenon was attributed to the activation of Kupffer cells, which may initiate the process of cellular inflammation.[27] Necrosis represents an advanced stage of hepatocyte degeneration. The onset of necrosis is characterized by pyknosis or alterations in nuclear morphology, which occur in response to the entry of highly concentrated toxic compounds into the cell. This infiltration induces severe conditions that compromise cellular integrity, leading to cellular swelling and a reduction in cell size.[28]

One of the antioxidant compounds in celery, apigenin, exhibits antioxidant effects by donating hydrogen ions in oxidation reactions, thus stabilizing reactive oxygen species and preventing lipid peroxidation. Apigenin also acts as a vasorelaxant or vasodilator, widening blood vessels through a calcium-antagonistic mechanism that inhibits vascular smooth muscle contraction induced by calcium release.[29]

The limitation of this study was that the preparation of liver tissue samples took an extended period of approximately two months, which may have led to tissue deterioration due to prolonged immersion in formalin. The findings of this study carry potential clinical implications, particularly for the development of preventive and therapeutic strategies against hepatotoxicity in humans. This research highlights the potential of ethanol extract from celery leaves in therapeutic applications, offering public health benefits. However, further clinical trials in humans are required to confirm its clinical applicability.

In future studies, testing of alanine aminotransferase (AST) and aspartate

aminotransferase (ALT) levels should be conducted to provide a more comprehensive assessment of liver function. Additionally, comparing histopathological changes in liver tissue before and after treatment will help determine the extent of damage more accurately throughout the treatment period.

CONCLUSIONS

Celery (*Apium graveolens*) demonstrates hepatoprotective effects in rats exposed to diethylene glycol (DEG)-induced toxicity, as evidenced by improvements in the histopathological profile of the liver.

Conflict of Interest

The authors declare no conflicts of interest concerning this study.

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Author Contributions

HE, SSW, NEE wrote the manuscript, designed the experiment and revised the manuscript, SSW analyzed the data, HE and SSW collected the research data in the laboratory. All authors have read and approved the final manuscript.

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Data Availability Statement

Data is available from the corresponding author upon request.

Declaration the Use of AI in Scientific Writing

We declare that we do not use AI in our scientific writing

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