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Nephroprotective and Hepatoprotective Effects of Turmeric in Diethylene Glycol Induced Toxicity in Rats

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ABSTRACT

In 2022, children in Indonesia experienced acute renal failure due to antipyretic syrup contaminated with diethylene glycol (DEG). DEG is a known contaminant in pharmaceutical solvents that can induce inflammation and act as a free radical, leading to kidney and liver damage. Turmeric (*Curcuma Longa*) has been reported to have nephroprotective and hepatoprotective effects due to anti-inflammatory and antioxidant properties. This study aims to evaluate the protective effects of turmeric ethanol extract on rat kidneys and liver subjected to DEG toxicity. Rats were divided into five groups (n=5 per group): Group I served as the normal control, while Group II received DEG orally at 3 g/kg BW twice daily for three days. Groups III, IV, and V were treated with DEG (3 g/kg BW) along with turmeric ethanol extract at a dose of 100, 200, and 400 mg/kg BW, respectively, administered orally twice daily for six days. After 14 days, all rats were sacrificed for macroscopic and microscopic evaluation using hematoxylin-eosin (H&E) staining. The results showed that rats treated with turmeric extract exhibited significantly significantly less kidney and liver damage ($p<0.05$). Kidney protection was evidenced by improvements in endothelial tissue, glomeruli, and tubules, while liver protection was indicated by reduced Kupffer cell activation, sinusoidal dilatation, hepatocyte degeneration, and necrosis. In conclusion, turmeric ethanol extract effectively protects against DEG-induced kidney and liver toxicity in rats.

Keywords: diethylene glycol; histopathology; rat; turmeric.

INTRODUCTION

The kidneys and liver play crucial roles in the body's main excretory and metabolic processes. Chemical-induced damage to these organs, such as nephrotoxicity and hepatotoxicity, can occur due to the formation of toxic metabolites that lead to cell death. Diethylene glycol (DEG) is a toxic compound known to cause nephrotoxicity and hepatotoxicity, primarily through the the formation of toxic metabolites, diglycolic acid (DGA). This metabolite generates free radicals that can damage cellular lipid membranes. DEG toxicity typically presents with symptoms of mild metabolic acidosis such as nausea and vomiting, which can progressively worsen and lead to severe kidney and liver damage (BPOM, 2023; Carsarett & Doull, 2021; Snellings et al., 2017).

DEG contamination in syrup products can occur as impurities in solvents like polyethylene glycol (PEG), propylene glycol (PG), sorbitol solution, glycerin/glycerol, and maltitol solution (BPOM, 2023; Jain et al., 2021; Sosa et al., 2014). In 2022, a case of atypical progressive acute kidney injury was reported in a child following the consumtion of antipyretic syrup in Indonesia, with DEG poisoning suspected as a potential cause. By December 5, 2022, the Indonesian Ministry of Health reported 324 cases of mysterious acute kidney injury in children across 27 provinces (BPOM, 2023). Similar incidents of DEG poisoning have occurred in Panama (2006) and Nigeria (2008), where DEG-contaminated paracetamol syrups caused fatal cases of acute kidney injury in children (Sosa et al., 2014). DEG induce inflammation and oxidative stress, exacerbating damage to both the kidneys and liver.

Herbal remedies have long been used as complementary medicine to address inflammation and oxidative stress caused by free radicals, including those from DEG (Okaiyeto et al., 2018). Turmeric (*Curcuma longa* Linn.), a medicinal plant, contains curcumin, a bioactive compound with anti-inflammatory and antioxidant properties (Fan et al., 2017; Hosseini & Hosseinzadeh, 2018; Kusbiantoro, 2018; Jabczyk et al., 2021). Studies have shown that curcumin exerts protective effects against liver damage induced by chemotherapy, $CuSO_4$, and CCl_4, as demonstrated by improved serum antioxidant defenses and histopathological changes in rats (Hashish & Elgaml, 2016; Hewlings & Kalman, 2017; Ibrahim et al., 2020; Ruiz de Porras et al., 2023). Additionally, turmeric ethanol extract has demonstrated renal protective effects

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in rats, mitigating the toxic effects of cyclosporine, cisplatin, and adenine, as indicated by decreased serum creatinine levels and tissue repair (Ali et al., 2018; Ortega-Domínguez et al., 2017; Kadhim et al., 2021).

This study aims to evaluate the protective effects of turmeric ethanol extract on DEG-induced kidney and liver damage in rats by conducting histopatological examinations of these organs. By investigating turmeric's role in mitigating DEG-induced toxicity, this research seeks to explore its potential as a natural therapeutic agent for preventing or reducing damage to vital organs.

MATERIALS AND METHOD

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 sonde, and syringes for oral administration of turmeric ethanol extract and DEG.

For histological preparation, the following tools were used: cover glasses, object slides, tissue cassettes, a rotatory microtome (Shandon AS 325, United Kingdom), styrofoam, histoplast, a paraffin dispenser, and a light microscope (CX23, China). The materials for histology 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).

Curcuma longa Linn. powder was obtained and has been authenticated from the Testing Laboratory-Unit Functional Services Traditional Health, Tawangmangu, Central Java. Other materials included DEG (Merck KGaA, Germany), 96% ethanol (Merck ETHANOL 96% REAG, Germany), Tween 80, and standard rat feed.

Methods

Preparation of Turmeric Extract

A total of 1000 grams of turmeric 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.

Experimental Animals

Male Sprague Dawley rats (2 months old, weighing 200 grams) were obtained from the Faculty of Pharmacy, Muhammadiyah Purwokerto University, Purwokerto, Indonesia. The rats were were acclimatized for five days, given standard pelleted feed and water ad libitum, and maintained on a 12:12-hour light-dark cycle. The animal experiments were approved by Ethics committee of Faculty of Health Sciences, Jenderal Soedirman University, with ethical approval number 1108/EC/KEPK/V2023.

A post-only control group design was used for this experimental study. After acclimatization period, the rats were divided into five groups, with five rats per group. Group I (control group) received only food and water. Group II received DEG orally at 3 g/kg BW twice daily for three days. Groups III, IV, and V were treated with DEG (3 g/kg BW) and turmeric ethanol extract at doses of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW, respectively (Ibrahim et al., 2020). The turmeric 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.

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 at the Faculty of Medicine, Universitas Gadjah Mada.

Two trained researchers, under the guidance a pathologist, independently examined the specimens using a binocular microscope (Optilab microscope digital camera system) at 400x magnification.

Statistical Analysis

The difference in rat body weight across groups were analyzed to evaluate the relationship between treatments and weight changes. Kidney and liver damage scores were statistically analyzed using the Kruskall-Wallis, followed by the Mann-Whitney U test, with SPSS version 26.

Liver damage was scored based on the percentage of damage across four parameters: Kupffer cell activation, sinusoid dilation, hepatocyte degeneration, and necrosis. The scoring criteria as follows: 0 for normal, 1 for damage <30%, 2 for damage 30-50%, and 3 for damage >50% (Arsad et al, 2014). Kidney damage was assessed using the endothelial glomerular tubular interstitial (EGTI) scoring system, evaluating endothelial, glomerular, tubular, and interstitial tissue (Khalid et al., 2016).

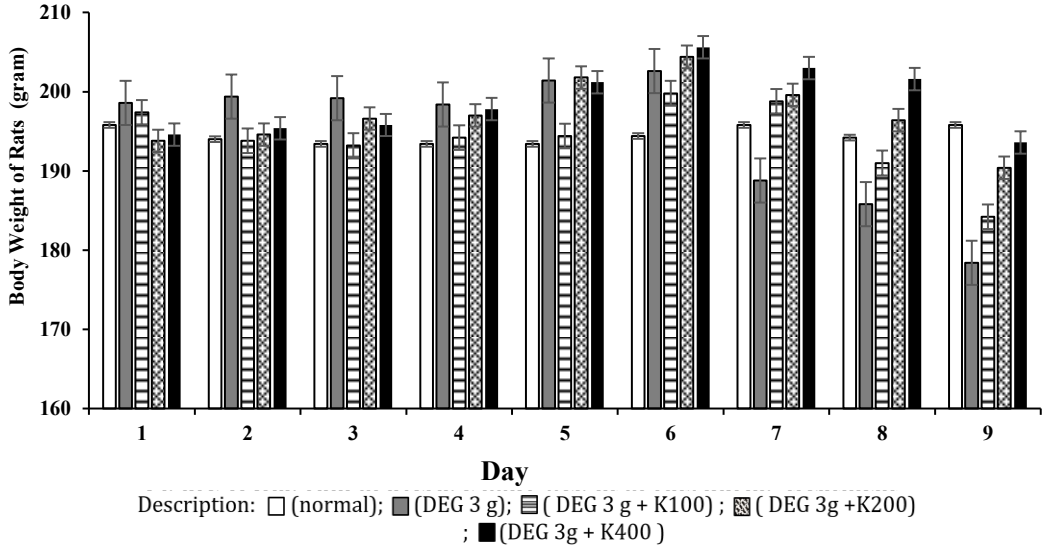

Figure 1. Diagram of average body weight of rats during treatment

RESULTS

Turmeric Extraction

Turmeric extraction was carried out using the maceration method, yielding 16.7%, which exceeds the 11% standard set by the Indonesian Herbal Pharmacopoeia. Maceration with 96% ethanol was selected to maximize curcumin extraction, as ethanol effectively dissolves curcumin without the need for heat, which could potentially degrade the compound. Additionally, ethanol evaporates quickly, aiding in the preservation of curcumin (Ningsih et al., 2020; Rezki et al., 2015).

Effect of DEG on Rat Body Weight

Changes in body weight were observed in rats fed standard feed, DEG, and DEG combined with turmeric ethanol extract (Figure 1). At the beginning of the study, there were no significant differences in body weight between the control and treatment groups ($p > 0.05$). However, by the end of the study, the group treated with DEG (3 g/kg BW) experienced a reduction in body weight. Although this decrease was not significantly different from the groups treated with DEG 3 and turmeric extracts at doses of 100, 200, and 400 mg/kg BW, it may be attributed to the toxic effects of DEG and stress-induced metabolic changes. Stress can trigger an imbalance in corticosterone production, leading to the breakdown of glucose and fat reserves, which in results in weight loss in rats (Agi & Titrawati, 2021).

Macroscopic Profile of Kidney and Liver

The macroscopic appearance of the kidneys and liver from rats treated with DEG (3 g/kg BW) and DEG combined with turmeric extract at doses of 100, 200, and 400 mg/kg BW are shown in Figures 2 and 3. In the normal group, the kidneys appeared normal, with a healthy brownish-red (brick red) color and smooth, pea-like shape (Agi & Titrawani, 2021). In contrast, the kidneys in the DEG 3 g/kg group showed discoloration, turning yellowish-brown. Similarly, the liver of the DEG-treated group exhibited a yellowish-brown, likely due to exposure to the toxic effects of DEG. This yellowing in the liver may be caused by fat accumulation and blood flow within the organ (Adelia et al., 2022). These results suggest that DEG exposure alters the macroscopic profile of the kidneys and liver, while treatment with turmeric extract (100, 200, and 400 mg/kg BW) did not directly alter the color of these organs.

Histopathological Profile of Kidney and Liver

Histopathological analysis of the kidneys and liver from the normal, DEG 3 g/kg BW, and turmeric extract-treated groups (100, 200, and 400 mg/kg BW) are presented in Figures 4-8 and Figure 9. Tissues were fixed in 10% buffered neutral formalin (BNF). In the DEG 3 g/kg BW group, moderate damage was observed in the kidney's endothelial tissue, glomeruli, and tubules. The liver of the DEG-treated group exhibited severe pathological changes, including increased Kupffer cell activation, sinusoidal dilatation, hepatocyte degeneration, and necrosis. In comparison, the groups with DEG and turmeric extract showed less severe damage, indicating a potential protective effect of turmeric against DEG-induced organ damage.

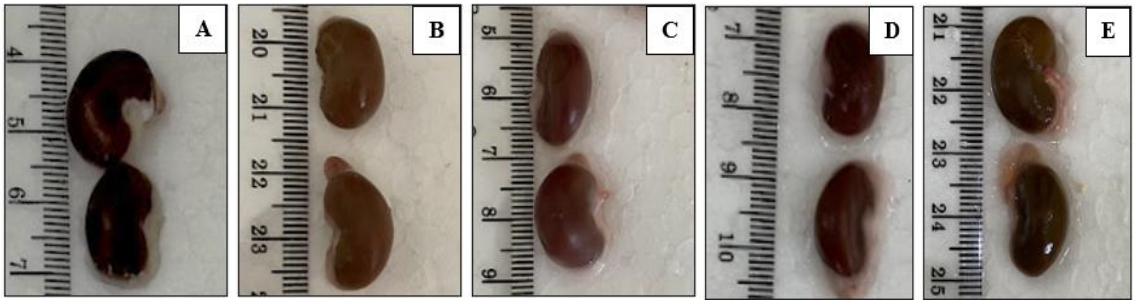

Figure 2. Macroscopic images of rat kidney organs from each group. (A) Normal group; (B) DEG 3 g group; (C) DEG 3 g + K100 group; (D) DEG 3 g + K200 group; (E) DEG 3 g + K400 group.

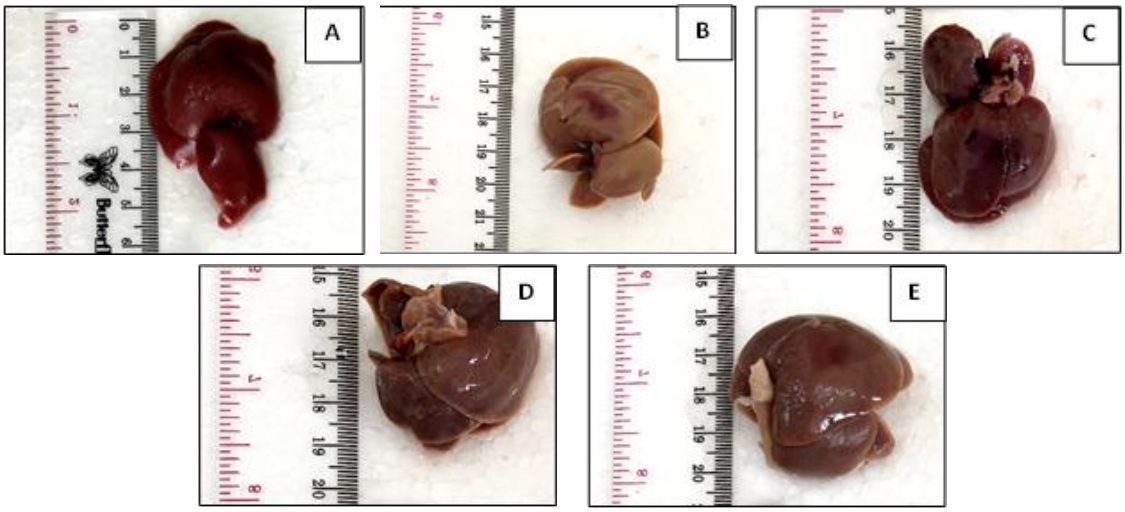

Figure 3. Macroscopic images of rat liver organs from each group. (A) Normal group; (B) DEG 3 g group; (C) DEG 3 g + K100 group; (D) DEG 3 g + K200 group; (E) DEG 3 g + K400 group.

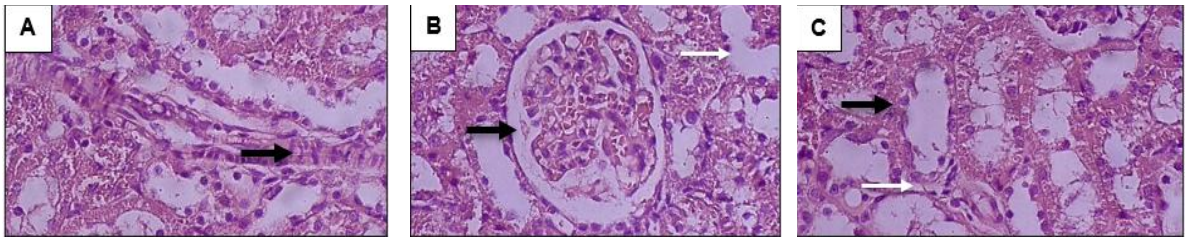

Figure 4. Kidney histopathology of the normal group with 400x magnification. (A) Normal endothelium, (B) Normal glomerulus (black arrow) and loss of tubule brush border (white arrow), (C) Normal tubule (black arrow), normal interstitial (white arrow).

DISCUSSION

The EGTI scoring of kidney histopathology (Table I) shows a significant difference in the endothelial tissue, glomeruli, and tubules between the DEG 3 g/kg BW group and both the normal and DEG + turmeric extract group. Damage to the kidneys from toxic substances can be observed through histological changes, including necrosis of proximal tubule epithelial cells, which are particularly sensitive to anoxia and prone to destruction by metabolic waste excreted through the kidneys (Jannah & Budijastuti, 2022). Acute kidney injury (AKI) is a complex process that leads to structural damage in the tubules, endothelium, glomeruli, and tubulointerstitial cells, as well as the loss of endothelial integrity and necrosis. Ischemia is a hallmark of AKI, driven by an imbalance between oxygen supply and demand, as well as impaired nutrient distribution and waste removal by the kidneys (Khalid et al., 2016; Rahman et al., 2016).

The primary DEG metabolite associated with renal failure is diglycolic acid (DGA), which is filtered in the glomeruli and transported into

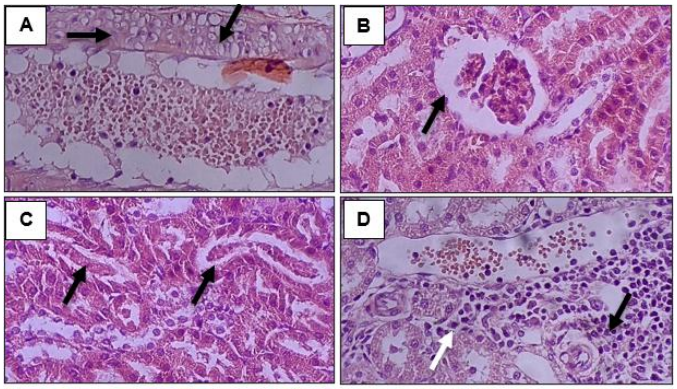

Figure 5. Kidney histopathology of 3 g DEG group with 400x magnification. (A) Endothelial swelling (black arrow), (B) Glomerular tuft retraction (black arrow), (C) Tubule necrosis (black arrow), (D) tubule inflammation (black arrow), interstitial inflammation (white arrow).

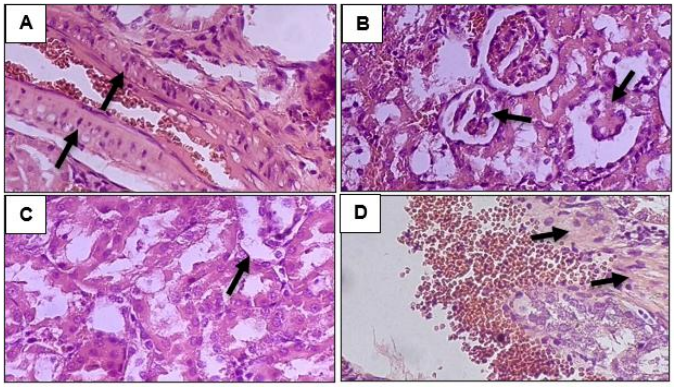

Figure 6. Kidney histopathology of DEG 3 g + K100 group with 400x magnification. (A) Endothelial swelling (black arrow), (B) Glomerular tuft retraction (black arrow), (C) tubule brush border loss (black arrow), (D) Interstitial inflammation (black arrow).

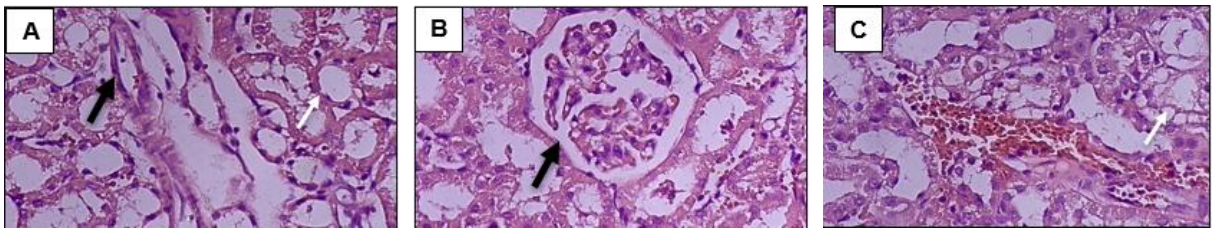

Figure 7. Kidney histopathology of DEG 3 g + K200 group with 400x magnification. (A) Endothelium without damage (black arrow) and tubules without damage (white arrow), (B) Retraction of glomerular tuft (black arrow), (C) Loss of tubular brush border (white arrow).

proximal tubule cells by sodium dicarboxylate transporters-1. DGA inhibits citric acid cycle enzymes, particularly succinate dehydrogenase, leading to cell death due to the inability to produce adenosine triphosphate (ATP) (Simorangkir & Suharjono, 2023). DGA also causes epithelial cell edema, obstructing the renal tubular lumen, reducing urine flow, and resulting in anuria and uremia (Jamison et al., 2021). The necrosisobserved in tubular epithelial cells of the DEG 3 g/kg BW group is likely due to the nephrotoxic effects of DEG, which induces widespread inflammation and damage to kidney tissues (Rafe et al., 2020).

Curcumin's antioxidant properties play a critical role in mitigating reactive oxygen species (ROS) formation, such as superoxide anions, hydrogen peroxide (H_2O_2), and nitrite radicals, which are activated by macrophages during inflammation. Curcumin and its

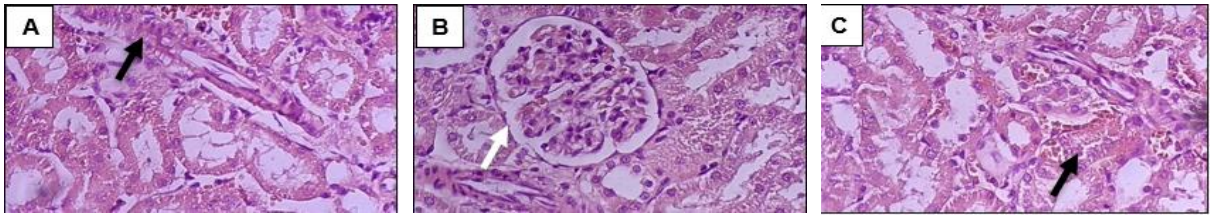

Figure 8. Kidney Histopathology of DEG 3 g + K400 group with 400x magnification. (A) endothelial swelling (black arrow) & interstitial inflammation (white arrow), (B) glomerulus without damage (white arrow), (C) tubule basement membrane thickening (black arrow).

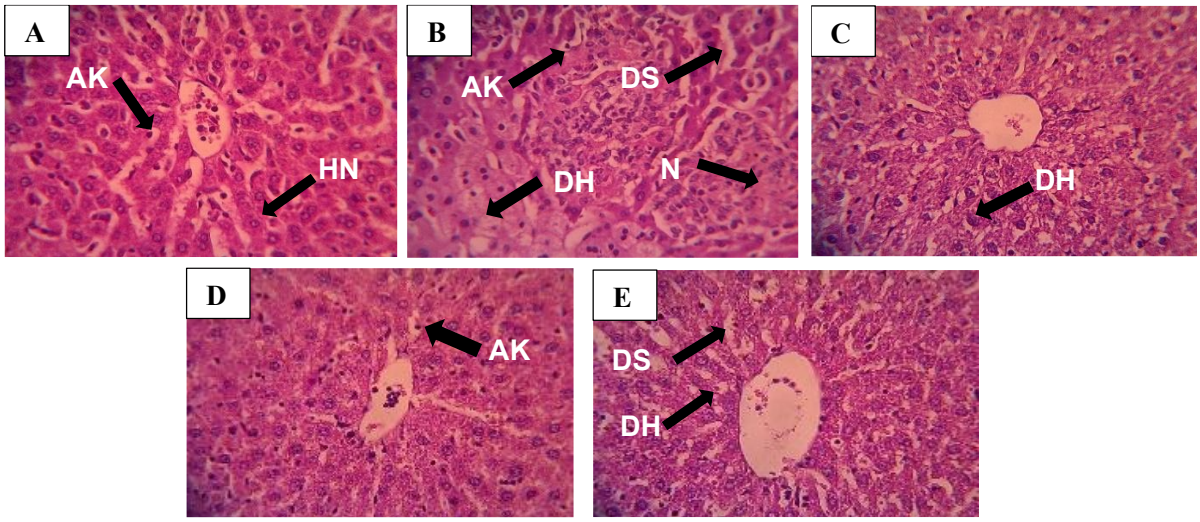

Figure 9. Histological evaluation on the liver of control and experimental groups. Rats were divided into 5 groups, (A) Normal control group; (B) DEG 3 g; (C) DEG 3 g + K100; (D) DEG 3 g + K200; (E) DEG 3 g + K400. Description: Normal hepatocytes (HN); Kupffer cell activation (AK); Sinusoid dilatation (DS); Hepatocyte degeneration (DH); N (necrosis). Magnification 400x.

Table I. Average Rats Kidney Histopathology EGTI Scoring Results & SEM

Group	Average Scoring EGTI & SEM			
	Endothelial	Glomerulus	Tubule	Interstitial
Normal	0.04 ± 0.04	0.24 ± 0.16	0.08 ± 0.08	0.08 ± 0.08
DEG 3 g	0.24 ± 0.04*	1.60 ± 0.13*	1.60 ± 0.09*	0.24 ± 0.12
DEG 3 g + K100	0.24 ± 0.04*	0.32 ± 0.23	0.12 ± 0.12	0.08 ± 0.05
DEG 3 g + K200	0.08 ± 0.05	0.24 ± 0.16	0.08 ± 0.05	0.04 ± 0.04
DEG 3 g + K400	0.04 ± 0.04	0.16 ± 0.09	0.04 ± 0.04	0.00 ± 0.00

The significance of $p < 0.05$ is indicated by the symbol (*)

derivatives—demethoxycurcumin and bis-demethoxycurcumin—demonstrate strong antioxidant activities that protect renal tubules from free radical damage and increasing the body's antioxidant defense system (Gani et al., 2021).

Various studies have confirmed turmeric's nephroprotective properties. For example, Ali *et al.* (2020) demonstrated that turmeric extract at a dose of 150 mg/kg BW exhibited antioxidant, anti-inflammatory, and anti-apoptotic effects on adenine-induced chronic renal failure in rats, as well as significantly reducing nephrotoxicity markers and improving kidney structure and function (Motaharinia et al., 2019). Similarly, Kaur et al. (2016) found that turmeric extract at 60 mg/kg BW significantly improved oxidative stress parameters and histological changes in kidney tissue of rats with renal failure. These findings align with our study, where turmeric doses of 100, 200, and 400 mg/kg BW showed nephroprotective effects (Fan et al., 2017; Thuawaini et al., 2019). Clinically, turmeric has also been shown to reduce oral mucositis in head and neck cancer patients undergoing radiochemotherapy (Dharman et al., 2021).

Table II. Average liver cell damage

Group	Kupffer cell activation	Sinusoidal dilatation	Hepatocyte degeneration	Necrosis
Normal	1 ±0.00	0.16 ±0.08*	1.28 ±0.30*	0.00 ±0.00*
DEG 3 g	1.16 ±1.67	1.4 ±0.54	2.68 ±0.22	0.76 ±0.69
DEG 3 g + K100	0.96 ±0.89*	0.76 ±0.21*	1.32 ±0.52*	0.2 ±0.28
DEG 3 g + K200	0.96 ±0.89*	0.56 ±0.38*	1.08 ±0.10*	0.00 ±0.00*
DEG 3 g + K400	0.92 ±0.08*	0.68 ±0.22*	1.32 ±0.60*	0.00 ±0.00*

Significance of $p < 0.05$ marked with symbol (*) compared with DEG 3 g group

The liver histopathology scoring (Table II) follows criteria of Arsad et al. (2014), assessing damage based on Kupffer cell activation, sinusoidal dilatation, hepatocyte degeneration, and necrosis. The DEG 3 g/kg BW group showed significantly more severe liver damage ($p<0.05$) than the the DEG 3 g + turmeric extract groups. The damage is caused by the accumulation of DGA in the liver, which produces ROS that trigger lipid peroxidation and compromise cell membraine integrity, leading to cell swelling and lysis (Robinson et al., 2017; Riset et al., 2022).

Previous study has shown that curcuminoids from turmeric, at doses of 75, 150, and 300 mg/kg BW, provide hepatoprotective effects in CCl_4-induced liver injury, as indicated by increased antioxidant defense markers (SOD, GSH, and catalase) and reduced liver damage biomarkers (AST, ALT, and ALP) (Ibrahim et al., 2020). Additionally, turmeric extract at doses of 200 and 400 mg/kg BW significantly liver histopathology damage in thioacetamide (TAA)-induced liver injury, as evidenced by decreased hepatocyte necrosis and parenchymal degeneration (Utami et al., 2022).

These results are in line with our findings, where turmeric extract reduced liver damage caused by DEG exposure, likely due to curcumin's antioxidant capacity, which prevents lipid peroxidation by donating hydrogen ions to stabilize ROS (Utami et al., 2022). Furthermore, curcumin increases the activity of antioxidant enzymes, such as SOD, GSH, and catalase, providing a defense against free radical damage (Hosseini & Hosseinzadeh, 2018). Curcumin's an anti-inflammatory properties, particularly its ability to inhibit the NF-κB pathway, reduce TNF-α expression, thereby minimizing inflammation in liver tissues (Supriono et al., 2019). However, a limitation of our study is the lack of detailed mechanistic insights into how turmeric inhibits lipid peroxidation or enhances antioxidant enzyme activity, such superoxide dismutase (SOD), in the context of DEG toxicity.

Interestingly, in the necrosis damage criteria, the group receiving 100 mg/kg BW turmeric extract showed improvement, although the difference was not statistically significant ($p>0.05$) compared to the DEG 3 g/kg BW group. This suggests that the 100 mg/kg BW dose may not be optimal for liver protection. The protective effects of curcumin on the liver are dose-dependent, with higher doses providing better protection, although care must be taken to avoid the maximum safe dose (Supriono et al., 2019).

CONCLUSION

Turmeric (*Curcuma longa*) exhibits nephroprotective and hepatoprotective effects in rats subjected to DEG-induced toxicity, as demonstrated by improvements in histopathological profiles of the kidney and liver.

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