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The efficacy of sap obtained from *Commiphora gileadensis* against cadmium-induced hepatorenal toxicity in male rats

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Abstract: Cadmium (Cd), a toxic heavy metal, ranks among the top ten environmental threats to human health, adversely affecting vital organs such as the central nervous system, kidneys, liver, pancreas, lungs, and testes. The antioxidant potentials of *Commiphora gileadensis* (CG) sap *in vitro* were estimated by the total phenolic and flavonoid content, DPPH (2,2-diphenyl-1-picrylhydrazyl radical-scavenging activity) and ABTS (2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid) free radical scavenging. The reducing activities were also assessed using copper (cupric reducing antioxidant capacity, CUPRAC) and ferric (ferric reducing antioxidant power, FRAP). The protective effects of the CG sap against Cd-induced liver and kidney damage in male rats were investigated *in vivo*. Forty-two healthy adult male albino rats were randomly divided into seven groups and treated for 60 days as follows: G1 (negative control), G2 (50 mg/l cadmium chloride in drinking water), G3 and G4 (100 mg/kg and 400 mg/kg CG sap, respectively), G5 (50 mg/l cadmium chloride + 100 mg/kg CG sap), G6 (50 mg/l cadmium chloride + 400 mg/kg CG sap), and G7 (1 % Tween 80, 1 ml/rat as a vehicle). The *in vitro* investigation revealed the potential antioxidant (DPPH, ABTS) and reducing (CUPRAC, FRAP) activities of the sap obtained from *Commiphora gileadensis*. Additionally, the *in vivo* experiment showed that cadmium exposure resulted in significantly increased malondialdehyde, reduced catalase and antioxidant capacities, and impaired liver and kidney functions. However, the co-administration of CG sap markedly ameliorated these adverse effects in a dose-dependent manner, improving the antioxidant capacity and restoring the hepato-renal function by improving the biochemical parameters and histological structure. It could be concluded that CG sap has the potential as a natural therapeutic agent to mitigate cadmium toxicity and its associated environmental hazards.

Keywords: antioxidants; heavy metals; histopathology; liver and kidney functions; medicinal plant

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The liver and kidneys are critical organs responsible for xenobiotic metabolism and storage, making them highly susceptible to damage from toxic substances. Cadmium (Cd), a non-essential transition metal, is a significant environmental contaminant known for its toxicity to humans and animals. Cd exposure occurs through industrial and agricultural activities, as well as contaminated food, water, and cigarette smoke (WHO 2010; Dharmadasa et al. 2017). Due to its long biological half-life (25–30 years), Cd bioaccumulates in tissues, primarily in the liver and kidneys, causing severe oxidative stress and tissue damage (Peng et al. 2018).

Cd toxicity is associated with various health complications, including hepatorenal syndrome, characterised by impaired liver and kidney functions and increased morbidity and mortality. The toxic effects of Cd are largely mediated by its induction of reactive oxygen species (ROS), leading to oxidative stress, mitochondrial dysfunction, and damage to cellular components (Liu et al. 2011; Genchi et al. 2020). Recently, the hazardous, deleterious effects of Cd on the central nervous system have been studied by many authors (Cirovic et al. 2025; Xie et al. 2025). Antioxidants, both synthetic and natural, have been investigated for their ability to counteract Cd-induced oxidative damage. Among the natural antioxidants, plant-derived compounds such as phenolics and flavonoids have shown significant protective effects (Ahmed et al. 2019; Cirovic et al. 2025).

Commiphora gileadensis (CG) L., a member of the Burseraceae family, is a small dioecious shrub growing naturally in the Red Sea area, the Mediterranean Basin, and areas bordering Saudi Arabia (Shalabi and Otaif 2022). Standing 2–4 m tall, it is characterised by a dark green, stout trunk; thin, peeling bark; and compound leaves arranged in alternating fascicles on short lateral branches (Eslamieh 2011; Yaniv et al. 2014). Traditionally known as the balm of Makkah, Mecca myrrh, opobalsam, or the biblical balm of Gilead, *C. gileadensis* has held profound cultural, religious, and medicinal value for millennia (Alhazmi et al. 2022). Its sap, bark, wood, leaves, flowers, and seeds have been integral to both Arabian folk medicine and Ayurvedic systems. Historical uses include the treatment of inflammatory conditions, gastrointestinal disorders (e.g., constipation and abdominal pain), joint ailments, headaches, coronary artery disease, gynaecological imbalances, and obesity (Alqethami et al. 2017). The plant's resin was particularly valued as a natural analgesic and a potent wound-healing agent, attributed to its beneficial effects on skin integrity and repair (Tajbakhsh et al. 2021; Althurwi et al. 2022; Alhazmi et al. 2022). Traditionally, CG sap has been used for its anti-inflammatory, antimicrobial, and wound-healing properties (Abdul-Ghani and Amin 1997; Al-Howiriny et al. 2004). Recent studies have highlighted the antioxidant potential of CG sap, which may offer protective effects against heavy metal toxicity (Bouslama et al. 2019; El Rabey et al. 2020). This study evaluates the ameliorative effects of CG sap on Cd-induced liver and kidney damage in male albino rats, with a focus on the histopathological changes and biochemical markers.

MATERIAL AND METHODS

Ethical approval

The current work was permitted by the Animal Ethics Committee of Qassim University (No. 100 24 902). All the experimental procedures were conducted in accordance with the institutional guidelines for animal welfare and care.

Commiphora gileadensis collection

Commiphora gileadensis was collected in Spring 2022 from a high-altitude location known as the Alaab Valley, located in the Al-Madinah region in the Western part of Saudi Arabia.

Preparation of *Commiphora gileadensis* sap

The growing tips of *C. gileadensis* branches were lopped, leaving a 5-mm distance from the tips. Subsequently, the exuding sap was promptly collected following the incision and stored at a temperature of –20 °C until it was ready for examination (Iluz et al. 2010).

In vitro assessment of the antioxidant activity

To evaluate the antioxidant activity, 1 g of plant sap was combined with 10 ml of ethanol. The

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mixture was agitated using a magnetic stirrer operating at 1 000 revolutions per minute (IKA, Staufen, Germany). Each parameter was examined in triplicate.

Determination of the total phenolic content (TPC)

The total phenolic content (TPC) was assessed through the Folin-Ciocalteu method (Slinkard and Singleton 1977), with gallic acid serving as the standard reference. In this procedure, 100 µl of either the standard or a blank plant sap sample was oxidised using 500 µl of a diluted Folin-Ciocalteu reagent. After a 5-minute reaction time, the mixture was neutralised by adding 1 ml of a sodium carbonate solution (7.5%, w/v) and then incubated for 120 min before the absorbance was measured at 765 nm. The results are expressed as milligrams of gallic acid equivalents (mg GAE/g).

Determination of the total flavonoid content (TFC)

The total flavonoid content (TFC) was evaluated using the aluminium chloride colorimetric technique, as outlined in a prior study (Chang et al. 2002). The absorbance was recorded at 405 nm. A calibration curve was created with quercetin as the standard, and the TFC was expressed in mg quercetin equivalents/g (mg QE/g).

Determination of the antioxidant activity using cupric reducing antioxidant capacity (CUPRAC)

The cupric reducing antioxidant capacity (CUPRAC) assay was conducted in accordance with the methodology established by Apak et al. (2004) and subsequently modified by Annapurna et al. (2021). Different concentrations of plant sap were combined with 1 ml of a 0.01 M Cu (II) chloride solution. Subsequently, 1 ml of a 7.5×10^3 M neocuproine solution and 1 ml of an ammonium acetate buffer at pH 7.0 were added. The mixture was then incubated in the dark at room temperature for 30 minutes. Following incubation, the absorbance of the resulting colour was measured at 440 nm using a reference blank. Trolox served as the standard antioxidant. The experiment was performed in triplicate, and the results were expressed as Trolox equivalents per gram of dry weight.

Measurement of the antioxidant activity via Ferric Reducing Antioxidant Power (FRAP)

The Ferric Reducing Antioxidant Power (FRAP) assay method was performed as described in accordance with the methodology outlined by Musa et al. (2015) to evaluate the antioxidant activity using Trolox as the reference standard. To prepare the FRAP reagent, a mixture was created using 300 mM acetate buffer, 10 mM TPTZ [2,4,6-tri(2-pyridyl)-*s*-triazine] dissolved in a 40 mM HCl solution, and 20 mM $FeCl_3 \cdot 6H_2O$, adhering to a volumetric ratio of 10 : 1 : 1. In the assay process, 1 900 µl of the FRAP reagent was combined with 100 µl of the sample, standard, or blank solution, and then incubated for 30 min before measuring the absorbance at 595 nm. The results were expressed as Trolox equivalents per gram of dry weight.

Determination of the antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging method

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay measures the reduction of the α-diphenyl-β-picrylhydrazyl radical by the antioxidants. This radical solution has a deep violet colour, which serves as the reference. Upon reduction, its colour intensity decreases. As a result, an inverse relationship is observed between the absorbance and the antioxidant concentration. The DPPH assay method described as indicated by Al-Altaie and Addai (2021) was used to evaluate radical-scavenging activity, using Trolox as the reference standard. During the experiment, 3 ml of the DPPH solution at a concentration of 40 mg/l was mixed with 100 µl of the sample, the standard, or a blank control. The mixture was then incubated for 30 min before the absorbance was measured at 517 nm. The results were expressed as Trolox equivalents per gram of dry weight.

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Determination of the antioxidant activity using the 2,2-azino-*bis*-3-ethyl-benz thiazoline-6-sulfonic acid (ABTS) free radical-scavenging method

2,2-azino-*bis*-3-ethyl-benz thiazoline-6-sulfonic acid (ABTS) is based on the generation of the green blue $ABTS^{\bullet+}$ radical, which can be reduced by the antioxidants. The reduction of the radical results in a decrease in the colour intensity of the solution, and this change is proportional to the reductant content in the test sample. The method for assessing the antioxidant activity, known as the Trolox equivalent antioxidant capacity (TEAC or ABTS) assay, was adapted from the procedure outlined by Ali et al. (2020). This technique uses Trolox as a reference standard. To produce ABTS radical cations, 7 mM of ABTS was oxidised with 2.45 mM of potassium persulfate, and the resulting solution was left in the dark at room temperature for 12 hours. The ABTS solution was then diluted with distilled water to achieve an absorbance of 1.000 ± 0.02 at 734 nm. A 1 ml portion of the ABTS cation solution was combined with 100 µl of the sample extract, standard, or blank, and the reduction in absorbance at 734 nm was recorded after 5 minutes. The results were expressed as Trolox equivalents per gram of dry weight.

Median lethal dose (LD_{50})

The LD_{50} of the CG sap was determined using twelve male Swiss albino mice (20–25 g). The mice were divided into four groups (n = 3 per group) and acclimated for seven days. Doses of 1.0, 2.5, and 5.0 g/kg body weight (b.w.) of CG sap in 1% Tween 80 were administered orally. Observations for mortality and behavioural changes were conducted for 48 h (Lorke 1983).

Animal experimentation

Forty-two adult male albino rats (200–220 g) were obtained from the Faculty of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The rats were housed in 50 × 30 × 25 cm plastic boxes with mesh wire covers for a period of 15 days to allow for adjustment. The recorded room temperature was 25 ± 2 °C, with a 12 h light/dark cycle and 60–70% humidity. The rats were provided with a standard pellet diet and with fresh water *ad libitum*. After a two-week acclimation period, the rats were randomly divided equally into seven groups (Table 1).

Rationale for animal model selection

The acute oral toxicity (LD_{50}) of the *Commiphora gileadensis* sap was determined in mice rather than rats in accordance with standard toxicological screening practices. Mice are commonly used for preliminary acute toxicity assessments due to their higher sensitivity to toxic substances, lower compound requirement, and well-established reference data for LD_{50} classification. The LD_{50} study was conducted solely to establish the safety margin of the *C. gileadensis* sap prior to its repeated-dose administration and was not intended for direct extrapolation to the rat efficacy model. Rats were subsequently selected for the sub-chronic hepatorenal toxicity and protection studies because

Table 1. Experimental design

Group	Treatment
NC (Group1)	normal drinking water and standard diet
Cd (Group 2)	50 mg/l cadmium chloride in the drinking water
CG1 (Group 3)	100 mg/kg CG sap orally
CG4 (Group 4)	400 mg/kg CG sap orally
CG1 + Cd (Group 5)	50 mg/l cadmium chloride + 100 mg/kg CG sap orally
CG4 + Cd (Group 6)	50 mg/l cadmium chloride + 400 mg/kg CG sap orally
V (Group 7)	1 ml of 1% Tween 80 orally

All the treatments were administered daily for 60 days. Cadmium chloride was supplied via the drinking water, while the CG sap and vehicle were administered orally by gavage (Kamel et al. 2011)

Cd = cadmium chloride; CG = *Commiphora gileadensis* sap; NC = negative control; V = vehicle

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they provide a more suitable and widely accepted model for biochemical, histopathological, and organ-specific toxicological evaluations.

Blood sampling

Blood samples were collected in test tubes from all rats per experimental group after euthanasia.

Serum preparation

Blood samples were centrifuged at ~1 509 × *g* for 15 min to separate the serum and stored at −80 °C until it was used for the biochemical analysis.

Biochemical analysis

Lipid peroxidation was calculated by measuring the malondialdehyde (MDA) levels following the procedure of Mahfouz et al. (1986). Briefly, thiobarbituric acid (TBA) reacted with MDA in an acidic medium at a temperature of 95 °C for 30 min to form the TBA reactive product; the absorbance of the resultant pink product can be measured at 534 nm.

The total antioxidant capacity (TAC) of the serum samples was assessed using the method designated by Benzie and Strain (1996). Briefly, the ferric reducing antioxidant power (FRAP) assay indirectly quantifies the antioxidant capacity, based on the reduction of Fe^{3+} (iron complex, yellow) to Fe^{2+} (iron complex, blue). The higher the antioxidant capacity of the analysed sample, the higher the Fe^{2+} concentration, and the more intense the absorbance at 630 nm. The catalase (CAT) activity was measured by the method described by Sinha (1972).

The alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total protein (TP), albumin (ALB), urea, creatinine, and uric acid were determined using commercially available kits (MyBioSource, San Diego, CA, USA).

Histopathological examination

Upon concluding the drug treatment phase, the rats from each group were euthanised. Following this, a thorough macroscopic assessment was performed as described by Aldaddou et al. (2022). Then, the liver and kidney samples were subsequently carefully removed and stored in a 10% buffered formalin solution. These tissues were thereafter dehydrated (in ethanol), cleared (in xylene), and infiltrated using paraffin wax (melting point 60 °C) in an oven maintained at a temperature of 62–65 °C. Blocks were prepared for sectioning by embedding the tissues in paraffin wax at 60 °C in metal moulds. Then, using a (Leica) rotary microtome, the tissues were sectioned at 5 µm and stained with the routine stain haematoxylin and eosin (H&E). DPX (Distrene 80, dibutyl phthalate, xylene) was placed on the section and then covered with a cover slip. Sections of the tissues were examined using a Leica light microscope (Japan) to assess the changes in the hepatorenal morphology, using the method outlined by Oda and El-Ashmawy (2012).

Statistical analysis

Data were expressed as the mean ± standard error (SE). Prior to applying the one-way analysis of variance (ANOVA), the assumptions of normality and homogeneity of variances were evaluated. The normal distribution of the data was assessed using the Shapiro–Wilk test, and the homogeneity of variances among the groups was verified using Levene's test.

After confirming that these assumptions were satisfied, the one-way ANOVA was performed to evaluate the influence of the seven treatment groups on the serum biochemical parameters (ALT, AST, ALP, total protein, albumin, urea, creatinine, uric acid) and antioxidant markers (MDA, catalase, and total antioxidant capacity). When significant differences were detected, Tukey's multiple-comparison post hoc test was applied to determine pairwise differences between the groups. Each group consisted of six biological replicates ($n = 6$). A value of $P < 0.05$ was considered statistically significant.

Statistical analyses were all performed using IBM SPSS Statistics software (v26.0; IBM Corp., Armonk, NY, USA). Values within each column that did not share a common superscript letter (a,b,c) were thus considered significantly different at $P < 0.05$.

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RESULTS

The median lethal dose (LD_{50}) of *C. gileadensis* sap

The findings indicated that none of the tested doses of *Commiphora gileadensis*, even at levels as high as 5 000 mg per kilogram of body weight, resulted in any fatalities within the various groups.

In vitro assessment of antioxidant properties

As illustrated in Figure 1, the *in vitro* assessment of the antioxidant activity revealed that the sap of *C. gileadensis* contained a high content of TPC (152.83 ± 3.24 mg GAE/g), TFC (87.92 ± 2.11 QE/g), had a high antioxidant potential of ABTS (96.70 ± 2.40 µmole TE/g) and DPPH

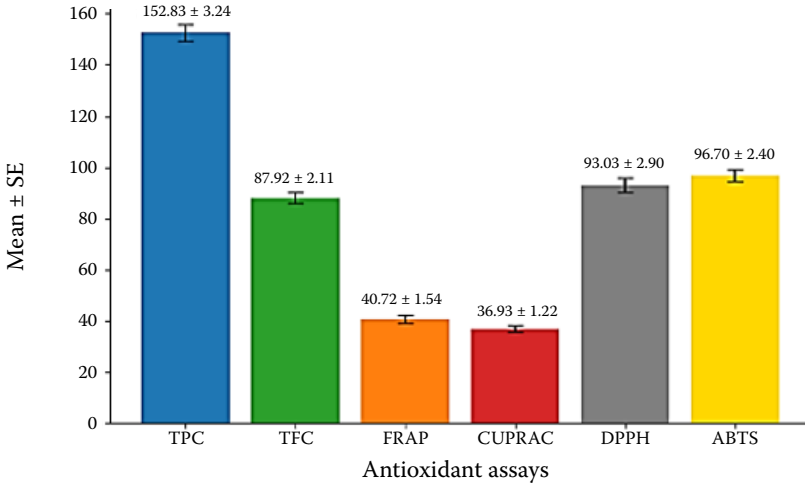

Figure 1. *In vitro* assessment of the antioxidant activity {TPC; CUPRAC; TFC; FRAP; DPPH; ABTS
Values are expressed as mean ± SE (each parameter measured in triplicate)
ABTS = 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid; CUPRAC = cupric reducing antioxidant capacity; DPPH = 2,2-diphenyl-1-picrylhydrazyl radical-scavenging activity; FRAP = ferric reducing/antioxidant power; SE = standard error; TFC = total flavonoid content; TPC = total phenolic content

Table 2. Effect of the CG sap, and cadmium chloride on the serum enzyme activities in rats

Group	TAC (mM/l)	MDA (nM/ml)	Catalase (U/l)	ALP (U/l)	ALT (U/l)	AST (U/l)
NC	0.52 ± 0.18^{a}	4.20 ± 0.34^{c}	887 ± 5.98^{a}	167.34 ± 9.00^{c}	72.23 ± 3.38^{c}	202.85 ± 04.82^{c}
Cd	0.09 ± 0.01^{b}	10.8 ± 2.66^{a}	673 ± 22.7^{b}	261.16 ± 8.35^{a}	144.83 ± 7.79^{a}	305.11 ± 15.03^{a}
CG1	0.49 ± 0.02^{a}	5.00 ± 0.57^{c}	822 ± 7.61^{a}	154.06 ± 12.22^{c}	72.47 ± 5.52^{c}	204.58 ± 07.30^{c}
CG4	0.66 ± 0.14^{a}	4.95 ± 1.16^{c}	802 ± 09.3^{a}	153.71 ± 08.57^{c}	77.40 ± 4.73^{c}	208.13 ± 16.29^{c}
CG1 + Cd	0.62 ± 0.04^{a}	8.11 ± 1.35^{b}	856 ± 32.5^{a}	206.84 ± 11.54^{b}	94.17 ± 3.58^{b}	246.80 ± 05.74^{b}
CG4 + Cd	0.48 ± 0.06^{a}	7.92 ± 0.91^{b}	863 ± 56.3^{a}	203.57 ± 14.03^{b}	99.73 ± 4.55^{b}	240.43 ± 10.38^{b}
V	0.53 ± 0.06^{a}	4.35 ± 0.42^{c}	889 ± 10.8^{a}	166.94 ± 19.12^{c}	71.03 ± 5.42^{c}	202.45 ± 08.01^{c}

$^{a–c}$Values within the same column carrying different letters are significantly different at $P < 0.05$, based on Tukey's post hoc multiple comparison test. Values are expressed as mean ± SE (n = 6 rats)
Group 1 (NC) received distilled water as a control. Group 2 (Cd) was given 50 mg cadmium chloride/l drinking water. Group 3 (CG1) was administered with 100 mg CG sap/kg. Group 4 (CG4) was administered with 400 mg CG sap/kg. Group 5 (CG1 + Cd) was administered with 100 mg CG sap/kg plus 50 mg cadmium chloride/l. Group 6 (CG4 + Cd) was administered with 400 mg CG sap/kg b.w. plus 50 mg cadmium chloride/l. Group 7 (V) was given 1 % tween 80, vehicle (1 ml/rat)
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Cd = cadmium chloride; CG = *Commiphora gileadensis* sap; MDA = malondialdehyde; NC = negative control; SE = standard error; TAC = total antioxidant capacity; V = vehicle

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(93.03 ± 2.90 μmole TE/g) radical-scavenging activities, and good metal chelating capacity as assayed by the FRAP (40.72 ± 1.54 μmole TE/g) and CUPRAC (36.93 ± 1.22 μmole TE/g) values.

Serum antioxidant indices

The data showed that the administration of *C. gileadensis* sap did not significantly affect the serum activity of catalase, total antioxidants, and malondialdehyde (MDA) compared to the values of the control groups (Table 2). The present data showed a significant ($P < 0.05$) decrease in the serum activity of the catalase enzyme and total antioxidants in the cadmium chloride-treated group compared to all the other groups of the study. While co-administration of *C. gileadensis* sap plus cadmium chloride significantly enhanced the serum activity of the catalase enzyme and total antioxidants, these values did not differ significantly from those of the control groups. The administration of cadmium chloride significantly increased the serum level of MDA compared to the other groups of the experiment. However, the co-administration of *C. gileadensis* sap significantly decreased the MDA level, but remained significantly higher than the control values (Table 2).

The liver function markers were analysed including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) as shown in Table 2. As can be observed from the table, a significant increase in AST, ALP, and ALT activities in the blood serum is clear in the Cd cohort, indicating the induction of liver injury. The effect and reduction of the liver function marker upon exposure to Cd suggest *C. gileadensis* contributes to the potential protective effect against liver injury in a dose-dependent manner.

Biochemical analysis

Further analysis of the other markers included albumin and total protein levels. The study results in Table 3 apparently indicate that the administration of Cd significantly decreases the serum total protein and albumin compared to all the other groups.

Meanwhile, co-administration of CG sap at 100 or 400 mg/kg with Cd significantly restored these parameters, but still below normal levels.

Eventually, the function and damage markers of the kidney were analysed as illustrated in Table 3. The analysis showed an increase in creatinine levels in the Cd cohort and urea and uric acid, which indicated the presence of kidney damage as a result of cadmium exposure. The effect and reduction of the kidney function marker upon exposure to Cd suggest *C. gileadensis* contributes to the potential protective effect against kidney injury in a dose-dependent manner.

Table 3. Effect of the CG sap, and cadmium chloride on the serum biochemical parameters in rats

Groups	Albumin (g/dl)	Total protein (g/dl)	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)
NC	3.65 ± 0.02^{a}	7.32 ± 0.16^{a}	0.20 ± 0.03^{c}	26.20 ± 0.72^{c}	2.59 ± 0.18^{b}
Cd	2.20 ± 0.15^{c}	4.31 ± 0.20^{c}	0.48 ± 0.05^{a}	41.80 ± 3.12^{a}	3.87 ± 0.18^{a}
CG1	3.62 ± 0.30^{a}	7.20 ± 0.05^{a}	0.22 ± 0.06^{c}	25.13 ± 5.80^{c}	2.01 ± 0.16^{c}
CG4	3.48 ± 0.33^{a}	7.20 ± 0.13^{a}	0.20 ± 0.05^{c}	23.67 ± 0.59^{c}	1.92 ± 0.35^{c}
CG1 + Cd	2.71 ± 0.11^{b}	5.27 ± 0.28^{b}	0.32 ± 0.01^{b}	33.57 ± 1.94^{b}	2.72 ± 0.11^{b}
CG4 + Cd	2.83 ± 0.17^{b}	5.07 ± 0.11^{b}	0.38 ± 0.04^{b}	33.64 ± 1.33^{b}	2.78 ± 0.33^{b}
V	3.57 ± 0.34^{a}	7.21 ± 0.17^{a}	0.23 ± 0.07^{c}	24.00 ± 0.30^{c}	2.63 ± 0.18^{b}

$^{a–c}$Values within the same column carrying different letters are significantly different at $P < 0.05$, based on Tukey's post hoc multiple comparison test. Values are expressed as mean ± SE ($n = 6$ rats)

Group1 (NC) received distilled water as a control. Group 2 (Cd) was given 50 mg cadmium chloride/l drinking water. Group 3 (CG1) was administered with 100 mg CG sap/kg. Group 4 (CG4) was administered with 400 mg CG sap/kg. Group 5 (CG1 + Cd) was administered with 100 mg CG sap/kg plus 50 mg cadmium chloride/l. Group 6 (CG4 + Cd) was administered with 400 mg CG sap/kg b.w. plus 50 mg cadmium chloride/l. Group 7 (V) was given 1% tween 80, vehicle (1 ml/rat)

Cd = cadmium chloride; CG = *Commiphora gileadensis* sap; NC = negative control; SE = standard error; V = vehicle

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Histopathological examination

The histological findings are depicted in Figures 2 and 3. No histopathological changes were detected in the examined livers of control rats (Figure 2A). The administration of Cd at 50 mg/l drinking water for 60 days induced a hazardous effect on the liver (Figure 2B,C). The liver histology of *C. gileadensis*

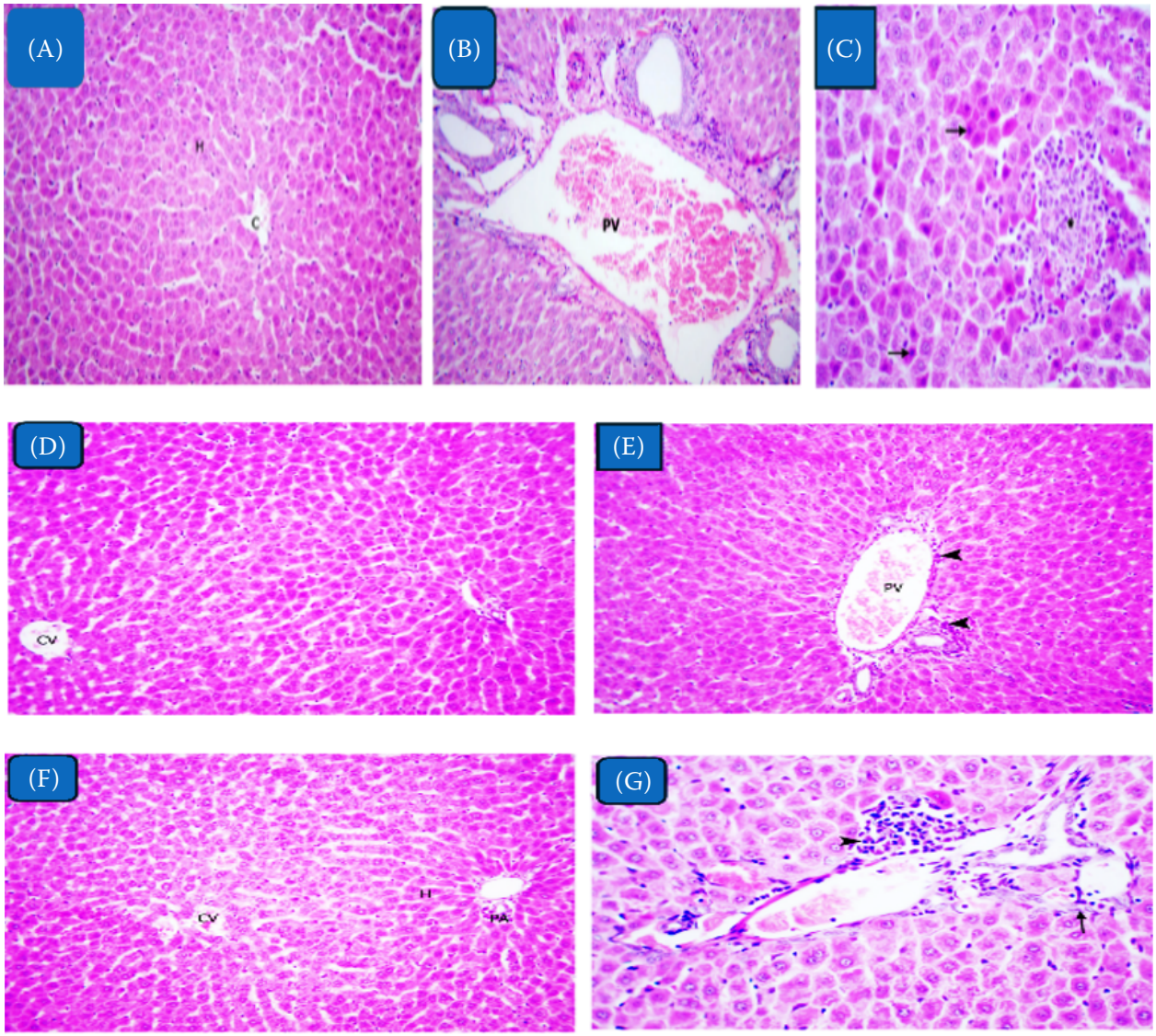

Figure 2. Effect of the CG sap, and cadmium chloride on the liver histology in rats
(A) Liver of a control rat showing the normal histological appearance of the central vein (C) and hepatocytes (H). H&E stain ×200. (B) Liver of a rat administered with 50 mg cadmium (Cd) showing congestion and dilatation of the portal vein (PV). (C) Liver of a rat administered with 50 mg cadmium (Cd) showing focal aggregates (asterisk) of lymphocytes and macrophages, individualised shrunken hepatocytes with hyper eosinophilic cytoplasm and pyknotic nuclei (arrow). H&E stain ×200. (D) Liver of a rat administered with 100 mg plant sap/kg b.w. showing mild congestion of the central vein (C) and the normal histological appearance of hepatocytes. H&E stain ×200. (E) Liver of a rat administered with 400 mg plant sap/kg b.w. showing congestion of the portal vein (PV) and mild lymphocytic (arrow) infiltrate in the portal areas. H&E stain ×200. (F) Liver of a rat administered with 400 mg plant sap/kg b.w. and 50 mg Cd showing mild congestion of the central vein (C) with the normal histological appearance of hepatocytes (H) and portal area (PA). H&E stain ×200. (G) Liver of a rat administered with 400 mg plant sap/kg b.w. and 50 mg Cd showing mild biliary hyperplasia and small numbers of lymphocytes (arrowhead) and macrophages in the portal areas. H&E stain ×400

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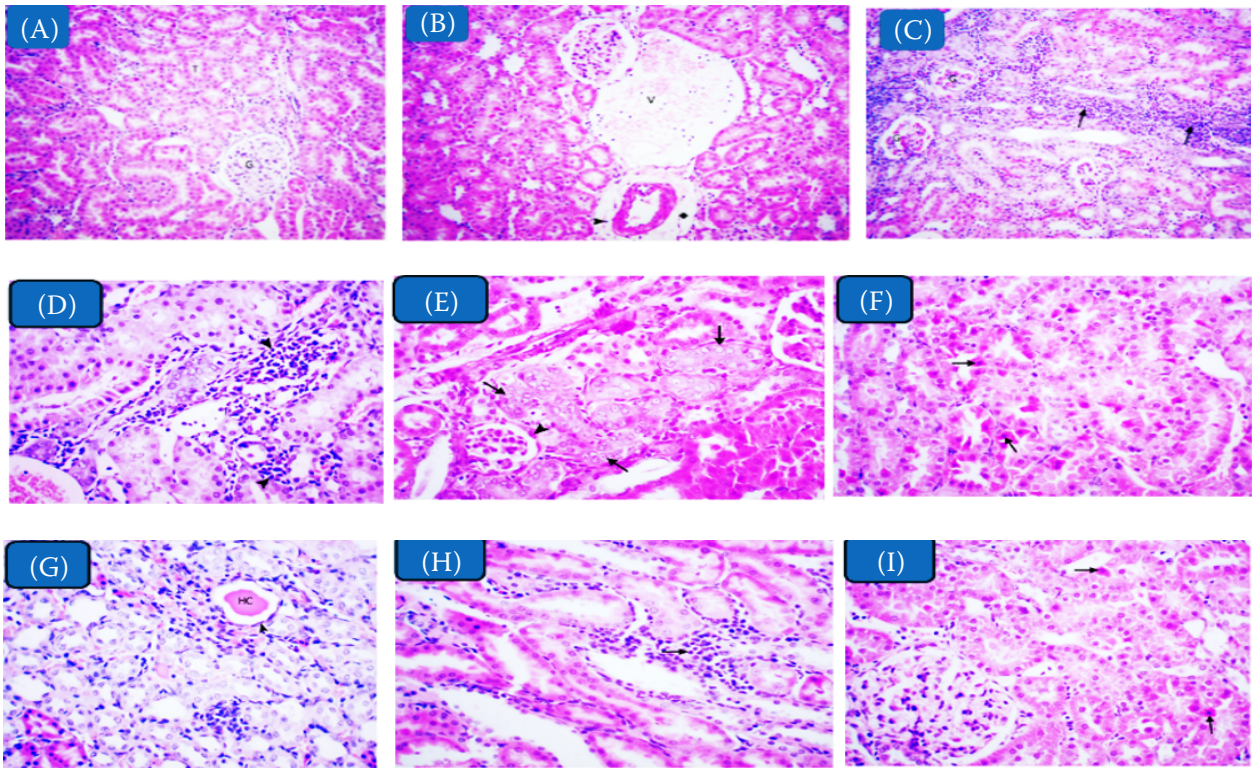

Figure 3. Effect of the CG sap, and cadmium chloride on the kidney histology in rats

(A) Kidney of a control rat showing the normal histological appearance of the glomerulus (G) and renal tubules (T). H&E stain ×200. (B) Kidney of a rat administered with 50 mg cadmium (Cd) showing congestion of the cortical blood vessel (V) with perivascular oedema (asterisk) infiltrated by a few lymphocytes (arrowhead). H&E stain ×200. (C) Kidney of a rat administered with 50 mg cadmium (Cd) showing interstitial lymphocytic (arrow) aggregates surround and replace tubules and glomeruli (G). (D) Kidney of a rat administered with 100 mg CG sap/kg b.w. and 50 mg Cd showing mild perivascular and intratubular lymphocytic aggregates (arrowhead). H&E stain ×200. (E) Kidney of a rat administered with 100 mg CG sap/kg b.w. and 50 mg Cd showing hypertrophy (arrowhead) of the parietal layers of Bowman's capsule. (F) Kidney of a rat administered with 100 mg CG sap/kg b.w. and 50 mg Cd showing coagulative necrosis of the lining epithelium of the proximal and distal convoluted tubule. (G) Kidney of a rat administered with 100 mg CG sap/kg b.w. and 50 mg Cd showing ectatic tubule lined by attenuated epithelium and contain eosinophilic homogeneous hyaline casts (HC) in the lumen. H&E stain ×400. (H) Kidney of a rat administered with 400 mg CG sap/kg b.w. and 50 mg Cd showing interstitial lymphocytic infiltrates in the renal cortex. H&E stain ×400. (I) Kidney of a rat administered with 400 mg CG sap/kg b.w. and 50 mg Cd showing the coagulative necrosis of tubular epithelium characterised by a loss of cellular detail, shrunken with hyper eosinophilic cytoplasm and nuclear pyknosis (arrow). H&E stain ×400

treated rats was not altered either with 100 mg/kg (Figure 2D) or 400 mg/kg CG4 (Figure 2E). While, the liver of *C. gileadensis* treated rats plus Cd, (CG4 + Cd) mitigated the hazard effect of Cd (Figure 2F,G).

The effects on the kidney's histology were similar. No histopathological changes were detected in the kidneys of control rats (Figure 3A). The kidneys of the Cd-treated rats (Figure 3B,C). The kidneys of *C. gileadensis* treated rats plus Cd, CG1 + Cd (Figure 3D–G). The kidneys of *C. gileadensis* treated rats plus Cd, CG4 + Cd (Figure 3H,I).

DISCUSSION

Cd accumulation occurs predominantly in the liver and kidneys, which serve as the primary sites for its toxic effects. Approximately 60% of the total body burden of cadmium is retained in these two organs (roughly 30% in each) while the remainder disperses to other tissues. Due to its slow elimination, cadmium exhibits an exceptionally long biological half-life, estimated at around 25 years (Genchi et al. 2020; Nordberg et al. 2021). This study is the first to explore the protective effects

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of *Commiphora gileadensis* (CG) sap against cadmium (Cd)- induced toxicity in liver and kidney tissues. Plants possess various bioactive compounds with significant antioxidant properties. Research on the antioxidant activity of diverse plant species may enhance our understanding of the potential of these species as sources of novel antioxidant compounds (But et al. 2024; Mittal et al. 2025; Zhu et al. 2025). Plants inhabiting extreme environments have developed a range of adaptive strategies. Among these strategies is the prevention of oxidative stress, which involves maintaining the ROS at non-hazardous levels. This highlights the need to examine the antioxidant properties of key plant species like *C. gileadensis*. Defensive mechanisms against oxidative stress are attributed to the natural antioxidants found in herbaceous plants and spices. These aromatic ingredients harbour compounds such as polyphenols, flavonoids, and phenolic compounds, which act as scavengers of free radicals (Zhao et al. 2025).

In the present study, the *C. gileadensis* sap exhibited strong antioxidant activity, as evidenced by its DPPH, ABTS, FRAP, and CUPRAC values. Some authors confirmed their previous findings on parts of the CG other than its sap, such as the leaves and bark. Ahmed et al. (2023) reported the DPPH value of CG to be 75.27%, which is lower than the value reported in this study. However, Ahmed et al. (2023) and Almulaiky and Al-Farga (2020) reported higher values, with the ABTS value of CG at 98, which is higher than the value obtained in this study. Similarly, TPC was assessed by Ahmed et al. (2023) and Safhi et al. (2022), and their values were 101.47 mg GAE/g and 92.54 mg GAE/g, respectively. Additionally, Safhi et al. (2022) reported the TFC value of CG to be 77.13 mg QE/g, which is lower than the value reported in this study. Furthermore, the highest antioxidant enzyme activity was present, with values of 16.87, 60.87, 35.76, and 27.98 U/mg for superoxide dismutase, peroxidase, catalase, and ascorbate peroxidase, respectively. Interestingly, Bin Mokaizh et al. (2024) utilised ultrasonic-assisted extraction in the CG leaves extract to improve the yield and recovery of phenolic compounds. They found that the TPC (mg GAE/g) and TFC (mg QE/g) were 96.55 and 31.66, respectively, and, through gas chromatography-mass spectrometry analysis, detected 25 phytochemicals not previously identified. Shadid et al. (2023) recorded that the steam-distilled essential oil of CG exhibited higher antioxidant activity than ascorbic acid. The major constituents in the essential oil were β-myrcene, nonane, verticiol, β-phellandrene, β-cadinene, terpinen-4-ol, β-eudesmol, α-pinene, cis-β-copaene and verticillol, which might be responsible for the antioxidant activity. However, there are no reports in the literature on FRAP and CUPRAC values. The differences between the results may be due to the geographical locations of the samples, the different portions used, and the extraction conditions, such as the methodology and diluents used in the extraction (Chaves et al. 2020; Safhi et al. 2022).

C. gileadensis sap has a wide safety margin, as confirmed in the present study, as the median lethal dose was above 5 g/kg b.w. These results align with the previous research conducted by Al-Mahbashi et al. (2015), who reported that *C. gileadensis* sap was safe up to 5 g/kg b.w. Consequently, any substance that demonstrates no harmful effects at a dosage of 5 000 mg/kg is categorised as being "practically non-toxic". Based on these outcomes, it can be concluded that *Commiphora gileadensis* sap is regarded as safe and practically non-toxic (Ecobichon 1997).

Cadmium is one of the most toxic heavy metals and affects both animals and humans by inducing cellular oxidative stress and subsequent elevation of free radicals. There is strong evidence suggesting that cadmium has a harmful effect on vital organs. The liver and the kidneys are the organs with the highest concentration of cadmium present after absorption (Nwokocha et al. 2012). When cadmium enters the body, it is transported into the bloodstream via erythrocytes and albumin and is then accumulated in the kidneys (Satarug 2018), liver, and gut (Tinkov et al. 2018a). Cadmium excretion from the body is slow and occurs via the kidneys, urine, saliva, and milk during lactation. Cd exposure can result in a variety of adverse effects, such as renal and hepatic dysfunction, central nervous system issues, pulmonary oedema, testicular damage, osteomalacia, and damage to the adrenals and heamopoietic system (Tinkov et al. 2018a; Cirovic et al. 2025; Xie et al. 2025). It has been proved that after exposure, Cd enters the blood and binds to the erythrocyte membranes and blood albumin and then is transported to the liver, where it binds to metallothionein (MT) (Tinkov et al. 2018b). The Cd-MT complex is then released back into circulation (Hambach et al. 2013) and accumulates in the

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blood system, kidneys, liver, lungs, testes, brain and bones (Charkiewicz et al. 2023; Cirovic et al. 2025; Xie et al. 2025).

In the current study, liver injury was evident in the Cd group, manifested by decreased total protein levels, increased liver enzymes, AST, ALT, and ALP. These results are in agreement with earlier studies (Almeer et al. 2019; Hamza et al. 2022). Recent reports have suggested that the lysosome instability caused by Cd toxicity resulted in the leakage of hepatic enzymes, including ALT, ALP and AST, into the bloodstream (Hamza et al. 2022). CG sap is a rich source of polyphenols. Polyphenols have been reported to possess a membrane stabilising activity by inhibiting the generation of ROS induced by Cd and maintaining the cell membrane structural integrity (Chen et al. 2016). Our findings exhibited an elevation in the liver enzymes in the Cd-treated group, which was in line with Toppo et al. (2015), who revealed that Cd toxicity causes hepatic cell damage and its enzymes AST, ALP and ALT are released into circulation; therefore, the activity of these enzymes in the blood is more elevated than normal. A histological examination of the liver tissue showed liver injury in the Cd-treated group, where the hepatocytes lost their characteristic regular arrangement. Most hepatocytes exhibited vacuolation, and their nuclei were partially pyknotic. In contrast, the CG co-treatment showed hepatic-protective effects, as evidenced by the restoration of liver structure and function in these groups. The hepatic-protective effects of the CG sap observed in this study support the opinion that CG restores the liver architecture and function following cadmium toxicity.

It is well known that when Cd is absorbed, it binds to serum proteins and is transported to the liver, where it is bound to metallothionein. The Cd-metallothionein complex is filtered in the renal glomerulus, Cd-metallothionein is reabsorbed in the tubular cells, and Cd is accumulated in the kidneys with a long biological half-life (Peng et al. 2018). Regarding kidney function, the increased levels of biomarkers (urea, creatinine, and uric acid) in our study reflected deterioration of kidney function following Cd exposure. The kidneys are dynamic organs that achieve critical biological functions by actively filtering excess fluid and secreting waste products including urea, uric acid, and creatinine (Rennke and Denker 2020). Our findings on the renal histology show severe congestion of renal blood vessels and extravasation of the RBCs among the glomeruli and proximal convoluted tubules. Degeneration and desquamation in the lining epithelium of proximal convoluted tubules were observed, some other tubules showed atrophy. These findings could be explained as Cd-induced nephrotoxicity mediated by the formation of Cd-Mt, which is constituted in the liver and released into the bloodstream. Cd-Mt was filtered by the renal glomeruli and taken up by the proximal convoluted tubular cells. This complex leads to tissue damage and the gradual loss of the kidneys' function (El-Refaiy and Eissa 2013). These histological abnormalities were found to be reduced in the CG + Cd groups. The co-treatments with CG led to the almost complete restoration of the Cd induced renal damage and restored the standard values of the kidney function markers.

Cd-induced hepatorenal dysfunction in this study was most likely due to an imbalance of the oxidant/antioxidant capacity in the tissues. The present study showed a significant increase in MDA levels and a decrease in the activity of antioxidant enzymes, such as serum total antioxidants and CAT. Conversely, the significant decline in MDA levels and elevations in the CAT and total antioxidant capacity in animals co-treated with CG sap indicate its capacity to suppress the cadmium-triggered oxidative degradation of membrane lipids, thereby offering hepatorenal protection. The serum malondialdehyde (MDA) is a non-invasive biomarker used to measure oxidative stress and lipid peroxidation in the body, where the MDA concentration correlates directly with the extent of membrane damage (Del Rio et al. 2002). The resulting oxidative damage interferes with critical cellular processes including enzymatic function, DNA repair, gene regulation, and signal transduction, ultimately disrupting the cellular redox balance. Endogenous antioxidants are important scavengers of free radicals, which eventually lead to cellular dysfunction and death (Ahmed et al. 2019). Serum CAT is a crucial antioxidant enzyme that protects cells by breaking down harmful hydrogen peroxide into water and oxygen, mitigating oxidative stress. The serum TAC measures the combined power of all the antioxidants in the serum to neutralise free radicals, offering critical protection against oxidative stress (Miller et al. 1993). Our findings agreed with previous reports demonstrating that cadmium induces kidney toxicity by enhancing the ROS formation and GSH consumption and inhibiting an antioxidant-mediated defence system (Shen et al. 2017; Genchi

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et al. 2020). The cadmium treatment significantly decreased the serum total proteins and albumin. Collecively, the hepatorenal damage might be produced by the acummulation of cadmium throught the liver and merely excreted through the kidney (Hamza et al. 2022; Elgharib et al. 2025). Cadmium exposure is tightly associated with renal dysfunction and kidney damage, causing polyuria and proteinuria (Vervaet et al. 2017). Additionally, the nephroprotective effect of CG was owed in a dose-dependent manner, is associated with the improvements in the renal architectures and decrease in the serum creatinine, urea and uric acid levels, which are consistent with Silveira et al. (2021).

Flora is used to cure several illnesses due to the wealth of antioxidants, which is a characteristic of traditional medicine (Mahmoudi et al. 2017). Antioxidants combat oxidation by attaching to the free radicals, chelating catalytic metals, reducing any Cd uptake (Winiarska-Mieczan 2015; Winiarska-Mieczan 2018), and scavenging oxygen (Akunna et al. 2017). Our results established that the *C. gileadensis* sap contains high levels of total phenolic and flavonoid content. In addition to higher ABTS radical-scavenging activity and the best DPPH scavenging activity, it showed good metal-chelating capacity as assayed by CUPRAC and FRAP. The co-administration of 400 mg/kg of CG sap restored the serum catalase to 863 ± 56.3 U/ml, comparable to the controls (887 ± 5.98 U/ml), and decreased the MDA levels by 28% relative to the Cd-only rats. Therefore, CG sap could potentially possess potent hepatorenal protective and antioxidative properties against cadmium toxicity.

Collectively, the administration of cadmium chloride induces adverse effects on liver and kidney functions and decreases the antioxidative status. The co-administration of CG sap with cadmium significantly mitigated the previous hazardous effects in a dose-dependent manner by ameliorating the antioxidant status. The plant sap showed no signs of toxicity during the acute toxicity study, and the LD_{50} value indicates that the sap is safe. A phytochemical investigation is also proposed to isolate the active fraction and eventually isolate a pure compound.

Conflict of interest

The authors declare no conflict of interest.

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