Experimental evaluation of *Curcuma Longa* in docetaxel-induced systemic toxicity: Functional hepatorenal and target organ analysis

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Abstract. Chemotherapy remains a cornerstone of cancer treatment; however, its clinical use is frequently limited by treatment-associated toxicities. This has prompted investigation into alternative adjuvant substances. *Curcuma longa*, a phytochemical with antioxidant and anti-inflammatory properties, may offer organoprotective effects. The present study therefore aimed to evaluate the protective effects of orally administered *C. longa* against docetaxel-induced systemic toxicity in Wistar rats. Male Wistar rats were assigned to five subgroups (n=7-group) and treated for 7, 14 or 21 days with placebo, docetaxel (2.5 mg-kg, intraperitoneally) or docetaxel combined with *C. longa* (25, 50 or 500 mg-kg-day, orally). Serum biomarkers of hepatic function (aspartate aminotransferase, alanine aminotransferase, bilirubins) and renal function (urea, creatinine, electrolytes) were evaluated using summary measures, ANOVA and Tukey's post-hoc tests, in addition to the relative weights of the liver, kidneys, heart, lungs and small intestine. Results indicated that docetaxel induced significant elevations in hepatic and renal biomarkers and altered organ weights. *C. longa* co-treatment attenuated these effects in a dose- and time-dependent manner. The 50 mg-kg dose consistently provided optimal protection. High-dose treatment was found to be associated with marked splenic and intestinal hypertrophy. Overall, *C. longa* demonstrated cytoprotective potential against docetaxel-induced toxicity. These findings were biologically consistent with antioxidant and anti-inflammatory mechanisms previously associated with curcuminoids.

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Introduction

Docetaxel is a widely used antineoplastic agent of the taxane class, with established efficacy in the treatment of numerous solid tumors, including breast, prostate and non-small cell lung cancers (1-6). Despite its therapeutic relevance, clinical use is often limited by dose-dependent systemic toxicities, particularly hepatotoxicity and nephrotoxicity, as well as off-target damage involving organs such as the spleen and intestine; these adverse effects have been associated with oxidative stress, inflammatory activation, mitochondrial dysfunction and impaired cellular metabolism (2-6).

In recent years, increasing attention has been directed toward natural compounds with antioxidant and cytoprotective properties as potential strategies to mitigate chemotherapy-induced toxicity. *Curcuma longa* L. (turmeric), traditionally used in Ayurvedic and Chinese medicine, contains bioactive polyphenols, including curcumin, that exhibit anti-inflammatory, hepatoprotective, nephroprotective

and immunomodulatory effects (7-11). Curcumin modulates intracellular signaling pathways involved in oxidative stress and inflammation, suppresses pro-inflammatory cytokines including TNF-α and IL-6, and attenuates oxidative damage in different models of tissue injury (12-17).

Despite the protective effects of *Curcuma longa* having been reported in models of chemotherapy-induced toxicity (3,4,8), notable mechanistic and translational gaps remain. The majority of previous investigations have focused on cisplatin- or doxorubicin-induced injury, while the biological effects of *C. longa* in docetaxel-induced systemic toxicity remain insufficiently characterized (8,15). Thus, limited evidence is available regarding its influence on hepatorenal dysfunction, electrolyte imbalance and target-organ remodeling during prolonged chemotherapeutic exposure. Furthermore, previous studies have rarely explored dose-dependent responses or the temporal progression of tissue injury and recovery (16,18).

With regard to cellular biology, docetaxel toxicity has been associated with the excessive production of reactive oxygen species, mitochondrial dysfunction, inflammatory signaling activation and apoptosis, all of which contribute to hepatocellular and renal tubular injury. These interconnected pathways have also been implicated in altering tissue homeostasis, vascular permeability and organ remodeling during systemic toxic stress (6,8,15,16). Understanding whether *C. longa* can modulate these biological mechanisms may contribute to the development of adjunctive strategies aimed at reducing chemotherapy-associated toxicity and preserving organ function. Therefore, the present study differed from previous investigations by simultaneously evaluating biochemical, functional and morphophysiological outcomes across a number of experimental timepoints and *Curcuma longa* doses, in a docetaxel-induced toxicity model. By integrating these parameters, the present study provided a broader interpretation of systemic toxicity progression and tissue adaptation during chemotherapeutic stress.

The aim was to evaluate the potential protective effects of orally administered *C. longa* extract against docetaxel-induced systemic toxicity in Wistar rats. Thus, the presen investigation focused on biochemical markers of hepatorenal function, electrolyte homeostasis, and morphophysiological alterations in target organs, including the liver, kidneys, spleen and small intestine. Particular attention was given to cellular and metabolic processes associated with oxidative stress, inflammatory activation and tissue remodeling during chemotherapeutic injury. It was hypothesized that oral administration of *C. longa* would attenuate docetaxel-induced systemic toxicity in a dose- and time-dependent manner by reducing hepatorenal dysfunction and preserving organ integrity. Intermediate and high doses of *C. longa* were also expected to provide greater cytoprotective effects compared with low-dose treatment.

Materials and methods

A total of 105 male Wistar rats (n=7 per subgroup; 8 weeks of age), obtained from the Piá dos Ratos Animal Facility (Colombo, Brazil), were involved in the present controlled experimental study. The methodological workflow employed is summarized in Fig. 1. Prior to the interventions, animals were randomly assigned to experimental groups to ensure an unbiased distribution across treatment conditions and experimental periods. The animals were then allocated into three primary groups according to treatment duration: Group A (7 days), Group B (14 days) and Group C (21 days). Each primary group was further subdivided into five treatment arms.

Subgroups G1A-G5A in Group A (7-day treatment) received treatments as follows: i) G1A: Oral placebo (water), daily for 7 days (control group); ii) G2A: Single intraperitoneal dose of docetaxel on day 1; iii) G3A: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 25 mg-kg-day; iv) G4A: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 50 mg-kg-day and; v) G5A: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 500 mg-kg-day.

Subgroups G1B-G5B in Group B (14-day treatment) received treatments as follows: i) G1B: Oral placebo (water), daily for 14 days (control group); ii) G2B: Single intraperitoneal dose of docetaxel on day 1; iii) G3B: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 25 mg-kg-day; iv) G4B: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 50 mg-kg-day and; v) G5B: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 500 mg-kg-day.

Lastly, subgroups G1C-G5C in Group C (21-day treatment) received treatments as follows: i) G1C: Oral placebo (water), daily for 21 days (control group); ii) G2C: Single intraperitoneal dose of docetaxel on day 1; iii) G3C: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 25 mg-kg-day; iv) G4C: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 50 mg-kg-day and; v) G5C: Single intraperitoneal dose of docetaxel on day 1 + *Curcuma longa* orally at 500 mg-kg-day.

In the docetaxel + *Curcuma longa* groups, *Curcuma longa* administration began on the same day as docetaxel exposure and continued once daily until the end of the assigned experimental period. Docetaxel was administered as a single intraperitoneal dose on day 1, whereas *Curcuma longa* was administered daily by oral gavage for 7, 14 or 21 days according to group allocation. To ensure comparable handling across groups, animals in the control and docetaxel-only groups received an equivalent volume of water by oral gavage throughout the corresponding experimental period.

The number of animals per subgroup (n=7) was defined based on previous experimental studies using similar designs, indicating that this sample size was sufficient to detect biologically relevant differences in biochemical and morphophysiological parameters while complying with ethical principles for animal experimentation (4,14,19-23). The present study followed the principles of the 3Rs, namely replacement, reduction and refinement, ensuring the minimum number of animals necessary to obtain statistically reliable results. To minimize observational bias, researchers responsible for biochemical analyses and organ weight measurements were blinded to treatment allocation during sample processing and data analysis. Animals were identified exclusively by coded labels throughout the present study, which were only decoded after completion of the statistical analyses.

The dose of docetaxel was extrapolated for rats using allometric scaling from a human reference (70 kg). Calculations

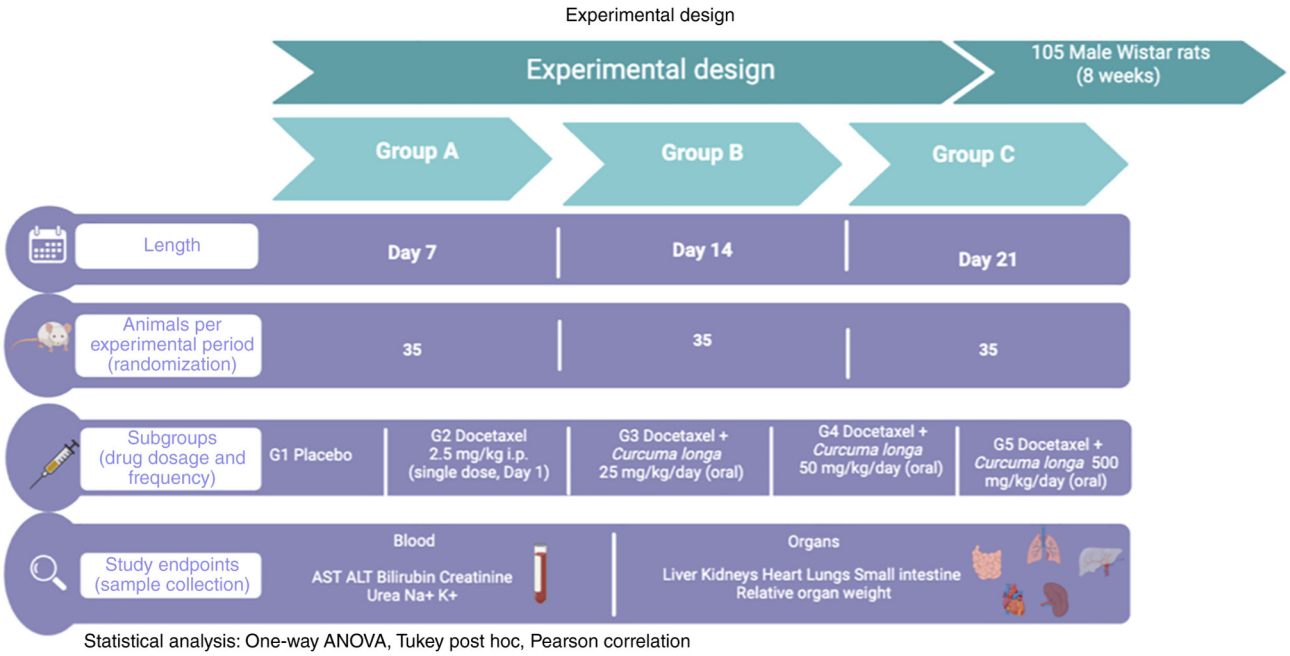

Figure 1. Methodological steps. i.p., intraperitoneal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

were based on specific metabolic rate (SMR) values: SMR_{ref} (human): $70x70^{-0.25}$=24 and SMR_{rat} (300 g): $70x0.3^{-0.25}$=95.

To reach the target dose in rats, the human equivalent dose was adjusted to 0.63 mg-kg. Thus, the rat dose=0.63-24x95=2.5 mg-kg. Therefore, a final intraperitoneal dose of 2.5 mg-kg docetaxel was established, in a volume up to 1 ml-kg. The administered dose was adjusted individually according to the body weight of each animal on the day of docetaxel injection. For example, for a 250 g rat, the following calculation would be applied: 2.5 mg-1000 g, X mg-250 g, thus X=0.625 mg.

The *Curcuma longa* extract (95% curcuminoids) was obtained from Farmácia Farmavida (Umuarama, Brazil) and administered by gavage at doses of 25, 50 or 500 mg-kg-day, diluted in 1 ml-kg of water. The selected doses were based on previous experimental studies demonstrating antioxidant, anti-inflammatory, hepatoprotective and nephroprotective effects of curcuminoids across low-, intermediate- and high-dose ranges in rodent models of drug-induced toxicity (4,13,14,17,19,21). The inclusion of numerous doses aimed to investigate potential dose-response associations and identify a therapeutic window capable of balancing cytoprotective efficacy with biological safety during prolonged exposure.

Animals were housed in polypropylene cages under controlled environmental conditions (22±2˚C; 12-h light-dark cycle) with free access to standard chow and water throughout the experimental period. Following treatment administration, animals were monitored continuously for the first 1 h, then hourly during the subsequent 6 h and thereafter once daily for 7, 14 or 21 days according to the respective experimental group, with attention to behavioral and clinical alterations. Animals were monitored daily for clinical signs of distress. Humane endpoints included severe lethargy, inability to access food or water, persistent recumbency, marked respiratory distress, self-mutilation, severe behavioral abnormalities or body weight loss >20% of baseline body weight. Any animal reaching these criteria would have been immediately euthanized to prevent unnecessary suffering. No animals met these predefined humane endpoint criteria during the present study.

At the end of each experimental period, animals underwent a 12-h fasting period with free access to water, were anesthetized with isoflurane 5% for induction of anesthesia prior to terminal blood collection from retro-orbital venous plexus and subsequent euthanasia by decapitation in accordance with the 2015 Brazilian National Council for the Control of Animal Experimentation (CONCEA) euthanasia guidelines (18).

Each biochemical parameter was measured once per animal and individual animal values were used for statistical analysis. A total of ~1 ml blood was collected from the retro-orbital venous plexus immediately after induction of anesthesia and prior to euthanasia. Following euthanasia, an additional 3-5 ml blood was collected for biochemical analyses. All samples were obtained at the end of the respective experimental period (7, 14 or 21 days).

The respective blood samples were collected for the assessment of hepatic function markers, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin, as well as renal function parameters, including urea, creatinine, sodium and potassium levels. Subsequently, the liver, kidneys, small intestine and heart were surgically excised, carefully cleaned of adherent tissues and weighed. Relative organ weight was calculated as the ratio between organ weight and final body weight and expressed as a percentage using the formula: Relative weight (%)=(organ weight-final body weight) x100. Carcasses were stored at -20˚C in labeled plastic bags until collection by a certified biological waste disposal company. Biological samples were homogenized and maintained at 4˚C until laboratory analysis.

All experimental procedures were approved by the Institutional Animal Care and Use Committee of Universidade Paranaense (Umuarama, Brazil; approval no. 40130) in 2023

Table I. Overall comparison of biochemical and organ body weight parameters according to experimental duration using ANOVA and Tukey's post-hoc tests.

Parameter	Variable	Group A (7 days)	Group B (14 days)	Group C (21 days)	P-value
Biochemical	Direct bilirubin	0.04±0.01[a]	0.03±0.02[b]	0.04±0.01[a,b]	0.0303[d]
	Indirect bilirubin	0.09±0.02[b]	0.12±0.04[a]	0.11±0.04[a]	0.0019[d]
	Total bilirubin	0.13±0.02[b]	0.15±0.03[a]	0.14±0.03[a,b]	0.0247[d]
	Creatinine	0.18±0.04[b]	0.41±0.17[a]	0.23±0.05[b]	<0.001[d]
	Potassium	5.13±0.59[a]	5.05±0.45[a]	5.07±0.48[a]	0.7943
	Sodium	133.71±5.15[b]	137.26±2.27[a]	136.69±2.4[a]	<0.001[d]
	AST	133.45±31[a,b]	142.62±35.42[a]	125.15±18.89[b]	0.0486[d]
	ALT	67.89±13.68[a]	72.93±15.23[a]	67.16±9.33[a]	0.1342
	Urea	39.52±4.18[b]	59.31±26.29[a]	44.34±5.86[b]	<0.001[d]
Organ body weight	Heart	1.05±0.12[a]	1.03±0.14[a]	1.09±0.23[a]	0.3177
	Liver	11.91±1.49[b]	11.65±2.58[b]	13.38±2.11[a]	0.0016[d]
	Intestine	1.7±0.55[a]	1.19±1.73[a]	1.27±1.67[a]	0.2771
	Body weight	348.91±40.84[a]	325.43±46.63[a]	349.83±50.07[a]	0.0465[d]
	Lung	2.14±0.59[a]	2.05±0.3[a]	2.44±1.08[a]	0.072
	Right kidney	1.02±0.12[b]	1.22±0.24[a]	1.16±0.17[a]	<0.001[d]
	Left kidney	0.99±0.12[b]	1.21±0.25[a]	1.14±0.17[a]	<0.001[d]

Values are presented as the mean ± SD. Data were analyzed using one-way ANOVA followed by Tukey's post hoc multiple-comparison test. [a], [b] and [ab] represent means within the same row sharing identical superscript letters that are not significantly different, whereas means with different superscript letters differ significantly (P<0.05). A, B and C represent the experimental time points.[d]Statistically significant differences at P<0.05. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

and conducted in accordance with the ethical and technical guidelines established by the 2015 Brazilian CONCEA (18).

Statistical analyses were performed according to the experimental design, which consisted of independent treatment groups evaluated at predefined time points. Continuous variables are expressed as the mean ± SD. Comparisons among groups were conducted using one-way ANOVA tests, followed by Tukey's post-hoc tests when statistically significant differences were identified. For within-period comparisons, one-way ANOVAs followed by Tukey's post-hoc tests were also used.

Given that animals evaluated at 7, 14 and 21 days represented independent subgroups rather than repeated measurements, time-dependent effects were interpreted through comparisons across independent experimental periods. Pearson's correlation coefficient was used to investigate associations between relative organ weights and biochemical markers as both variables were continuous and biologically associated with organ function. P<0.05 was considered to indicate a statistically significant difference. All analyses were performed using GraphPad Prism (version 10.4.2; Dotmatics) and R software (version 4.5.0; Posit Software, PBC).

Results

General analysis

Biochemical parameters. In the ANOVA conducted at a 5% significance level, significant differences among groups were observed for total bilirubin (P=0.0247), direct bilirubin (P=0.0303), indirect bilirubin (P=0.0019), creatinine (P<0.001), sodium (P<0.001), AST (P=0.0486) and urea (P<0.001), whereas potassium and ALT did not show significant variation (P=0.7943 and P=0.1342, respectively; Table I). Tukey's post-hoc test demonstrated that total bilirubin levels were higher in the 14-day group ($\bar{x}_{14}$=0.15; $\bar{\sigma}_{14}$=0.03) compared with the 7-day group ($\bar{x}_{7}$=0.13; $\bar{\sigma}_{7}$=0.02) while the 21-day group exhibited intermediate values ($\bar{x}_{21}$=0.14; $\bar{\sigma}_{21}$=0.03). Similarly, indirect bilirubin levels were significantly higher in the 14-day ($\bar{x}_{14}$=0.12; $\bar{\sigma}_{14}$=0.04) and 21-day groups ($\bar{x}_{21}$=0.11; $\bar{\sigma}_{21}$=0.04) compared with the 7-day group ($\bar{x}_{7}$=0.09; $\bar{\sigma}_{7}$=0.02). By contrast, direct bilirubin levels were lower in the 14-day group ($\bar{x}_{14}$=0.03; $\bar{\sigma}_{14}$=0.02) compared with the 7-day group ($\bar{x}_{7}$=0.04; $\bar{\sigma}_{7}$=0.01), whereas the 21-day group did not differ significantly from the others ($\bar{x}_{21}$=0.04; $\bar{\sigma}_{21}$=0.01).

Creatinine levels showed a marked elevation at 14 days ($\bar{x}_{14}$=0.41; $\bar{\sigma}_{14}$=0.17) relative to the 7-day ($\bar{x}_{7}$=0.18; $\bar{\sigma}_{7}$=0.04) and 21-day groups ($\bar{x}_{21}$=0.23; $\bar{\sigma}_{21}$=0.05), suggesting a transient phase of renal dysfunction during the intermediate stage of exposure. Sodium concentrations were also higher in the 14-day ($\bar{x}_{14}$=137.26; $\bar{\sigma}_{14}$=2.27) and 21-day groups ($\bar{x}_{21}$=136.69; $\bar{\sigma}_{21}$=2.4) compared with the 7-day group ($\bar{x}_{7}$=133.71; $\bar{\sigma}_{7}$=5.15). For AST, higher values were observed in the 14-day group ($\bar{x}_{14}$=142.62; $\bar{\sigma}_{14}$=35.42) relative to the 21-day group ($\bar{x}_{21}$=125.15; $\bar{\sigma}_{21}$=18.89), indicating greater hepatocellular stress during the intermediate phase of treatment. Finally, urea levels were significantly elevated in the 14-day group ($\bar{x}_{14}$=59.31; $\bar{\sigma}_{14}$=26.29) whereas the 7-day ($\bar{x}_{7}$=39.52; $\bar{\sigma}_{7}$=4.18) and 21-day groups ($\bar{x}_{21}$=44.34; $\bar{\sigma}_{21}$=5.86) did not differ significantly from each other (Table I).

Organ body weight parameters. ANOVA tests conducted at a 5% significance level demonstrated significant variation among groups for body weight (P=0.0465), liver weight (P=0.0016), right kidney weight (P<0.001) and left kidney weight (P<0.001), whereas heart, lung and intestinal weights remained statistically unchanged (P=0.3177; P=0.072; and P=0.2771, respectively). Post-hoc comparisons indicated that liver weight was greater in the 21-day group ($\bar{x}_{21}$=13.38; $\bar{\sigma}_{21}$=2.11) compared with the 7-day ($\bar{x}_{7}$=11.91; $\bar{\sigma}_{7}$=1.49) and 14-day groups ($\bar{x}_{14}$=11.65; $\bar{\sigma}_{14}$=2.58). For both kidneys, animals evaluated at 14 and 21 days showed increased mean values (right $\bar{x}_{14}$=1.22; $\bar{\sigma}_{14}$=0.24 and left $\bar{x}_{14}$=1.21; $\bar{\sigma}_{14}$=0.25; right $\bar{x}_{21}$=1.16; $\bar{\sigma}_{21}$=0.17 and left $\bar{x}_{21}$=1.14; $\bar{\sigma}_{21}$=0.17) relative to those observed at 7 days (right $\bar{x}_{7}$=1.02; $\bar{\sigma}_{7}$=0.12 and left $\bar{x}_{7}$=0.99; $\bar{\sigma}_{7}$=0.12). In relation to body weight, animals from the 14-day group exhibited a tendency toward lower mean values ($\bar{x}_{14}$=325.43; $\bar{\sigma}_{14}$=46.63); however, no statistically significant distinction was identified compared with the 7-day ($\bar{x}_{7}$=348.91; $\bar{\sigma}_{7}$=40.84) and 21-day groups ($\bar{x}_{21}$=349.83; $\bar{\sigma}_{21}$=50.07; Table I).

Analysis by period

Biochemical parameters. No statistically significant differences were identified among groups at 7 or 14 days. By contrast, at 21 days, significant variation was observed for potassium (P=0.0201) and urea levels (P=0.0078). Pairwise comparisons demonstrated that the CGC group exhibited higher potassium concentrations ($\bar{x}_{CGC}$=5.57; $\bar{\sigma}_{CGC}$=0.55) compared with the CG500 group ($\bar{x}_{CG500}$=4.80; $\bar{\sigma}_{CG500}$=0.23) whereas the remaining groups exhibited comparable values.

For urea, the CGQ group exhibited higher mean concentrations ($\bar{x}_{CGQ}$=49.99; $\bar{\sigma}_{CGQ}$=8.21) relative to the CG50 ($\bar{x}_{CG50}$=40.66; $\bar{\sigma}_{CG50}$=4.42) and CG500 groups ($\bar{x}_{CG500}$=40.72; $\bar{\sigma}_{CG500}$=1.81). Meanwhile, the CG25 and CGC groups remained at intermediate levels ($\bar{x}_{CG25}$=43.75; $\bar{\sigma}_{CG25}$=3.55 and $\bar{x}_{CGC}$=46.05; $\bar{\sigma}_{CGC}$=4.43, respectively). These findings suggest that prolonged exposure across 21 days was associated with distinct metabolic responses involving potassium regulation and nitrogen metabolism (Table II).

Organ body weight parameters. No significant differences were observed among groups at 7 or 14 days. However, after 21 days, significant variation emerged for body weight (P=0.0078), liver weight (P=0.0126), right kidney weight (P=0.0256) and left kidney weight (P=0.0425). Post-hoc analysis demonstrated that animals in the CG500 group showed lower body weight values ($\bar{x}_{CG500}$=309.86; $\bar{\sigma}_{CG500}$=35.19) compared with the CG25 group ($\bar{x}_{CG25}$=392.29; $\bar{\sigma}_{CG25}$=42.28). In relation to liver weight, the CG25 group presented higher mean values ($\bar{x}_{CG25}$=15.15; $\bar{\sigma}_{CG25}$=1.98) compared with both the CG500 ($\bar{x}_{CG500}$=12.05; $\bar{\sigma}_{CG500}$=1.25) and CGC groups ($\bar{x}_{CGC}$=11.99; $\bar{\sigma}_{CGC}$=1.69). A similar pattern was observed for renal weight, with lower mean values identified in the CG500 group (right $\bar{x}_{CG500}$=1.01; $\bar{\sigma}_{CG500}$=0.06 and left $\bar{x}_{CG500}$=1.00; $\bar{\sigma}_{CG500}$=0.06) and higher values in the CG25 group (right $\bar{x}_{CG25}$=1.26; $\bar{\sigma}_{CG25}$=0.09 and left $\bar{x}_{CG25}$=1.23; $\bar{\sigma}_{CG25}$=0.12). Thus, prolonged exposure was associated with differential morphophysiological responses according to *Curcuma longa* dose and duration of treatment (Table II).

Correlation between organ body weight and biochemical parameters. In the 7-day group, no statistically significant correlations were identified between mean kidney weight (right and left) and sodium (P=0.700), potassium (P=0.660) or urea levels (P=0.910). Similarly, no significant associations were observed between liver weight and total bilirubin (P=0.390), direct bilirubin (P=0.160), indirect bilirubin (P=0.180), AST (P=0.190) or ALT (P=0.290; Table III).

By contrast, the 14-day group demonstrated significant positive correlations between mean kidney weight and urea levels (r=0.80; P<0.010), suggesting that increased renal mass occurred alongside worsening nitrogen retention during the intermediate phase of toxicity. Significant associations were also observed between liver weight and total bilirubin (r=0.47; P<0.010), as well as between liver weight and indirect bilirubin (r=0.36; P=0.030), indicating an association between hepatic enlargement and altered bilirubin metabolism. No significant correlations were identified between kidney weight and sodium or potassium levels, nor between liver weight and direct bilirubin, AST or ALT (P≥0.05; Table III).

In the 21-day group, no significant correlations were detected at the 5% level. Despite this, certain variables showed a tendency toward association, including mean kidney weight with potassium levels (r=0.29; P=0.100) and liver weight with ALT (r=0.30; P=0.080), although these associations did not reach statistical significance (Table III).

Discussion

Docetaxel is a widely used chemotherapeutic agent with established antineoplastic activity against a number of solid tumors. However, its clinical utility is frequently limited by dose-dependent systemic toxicities, particularly hepatotoxicity and nephrotoxicity, which may compromise treatment adherence and overall patient outcomes. In the present study, docetaxel administration induced significant biochemical and morphophysiological alterations involving hepatic and renal function, consistent with previous experimental and clinical observations (16,18,19).

Co-treatment with *Curcuma longa*, specifically at intermediate and high doses, attenuated alterations in AST, bilirubin fractions, creatinine and urea levels. Despite ALT levels not differing significantly, a non-significant tendency toward normalization was observed, which may have still indicated a partial protective response against chemotherapy-associated organ dysfunction. The absence of statistical significance for ALT should therefore be interpreted with caution, as it does not necessarily exclude hepatotoxicity, particularly when other hepatic markers, such as AST and bilirubin fractions, showed alterations compatible with liver injury. Notably, the hepatotoxic effects observed in the present study may be more plausibly attributable to chemotherapy exposure compared with *Curcuma longa* intervention, since co-treatment tended to attenuate, rather than exacerbate, biochemical evidence of organ dysfunction. These findings are biologically consistent with the antioxidant and anti-inflammatory properties previously described for curcuminoids in experimental models (16,18,19). In addition, the protective responses observed in the present study were both dose- and time-dependent, with more evident effects occurring after prolonged exposure.

The attenuation of AST and bilirubin alterations in animals receiving *Curcuma longa* aligned with previous reports

Table II. Group comparison of biochemical and organ body weight parameters according to experimental duration using ANOVA and Tukey's post-hoc test.

A, Biochemical parameters

Time period	Variable	G25	G50	G500	GC	GQ	P-value
7 days	Direct bilirubin	0.04±0.01[a]	0.04±0.01[a]	0.04±0.01[a]	0.05±0.01[a]	0.04±0.01[a]	0.2516
	Indirect bilirubin	0.09±0.02[a]	0.09±0.02[a]	0.09±0.03[a]	0.08±0.03[a]	0.09±0.02[a]	0.7145
	Total bilirubin	0.13±0.02[a]	0.13±0.02 [a]	0.14±0.02[a]	0.13±0.02[a]	0.13±0.01[a]	0.9313
	Creatinine	0.2±0[a]	0.17±0.05[a]	0.19±0.04[a]	0.17±0.05[a]	0.19±0.04[a]	0.6271
	Potassium	5.14±0.36[a]	4.72±0.34[a]	4.99±0.42[a]	5.57±0.97[a]	5.22±0.39[a]	0.0885
	Sodium	136.71±2.29[a]	131.43±6.48[a]	135±3.37[a]	130.43±6.32[a]	135±4.32[a]	0.1034
	AST	156.86±15.98[a]	117.4±20[a]	120.44±30[a]	138.99±40.72[a]	133.56±32.55[a]	0.1113
	ALT	73.3±6.29[a]	67.43±17.96[a]	64.46±8.67[a]	66.03±19.95[a]	68.21±13.15[a]	0.8147
	Urea	40.85±2.43[a]	37.32±4.93[a]	37.99±3.05[a]	40.79±3.2[a]	40.67±5.96[a]	0.3228
14 days	Direct bilirubin	0.04±0.02[a]	0.02±0.02[a]	0.03±0.02[a]	0.03±0.03[a]	0.03±0.02[a]	0.4294
	Indirect bilirubin	0.11±0.04[a]	0.14±0.03[a]	0.13±0.04[a]	0.09±0.03[a]	0.12±0.03[a]	0.1463
	Total bilirubin	0.15±0.04[a]	0.16±0.02[a]	0.16±0.03[a]	0.13±0.04[a]	0.15±0.02[a]	0.2344
	Creatinine	0.51±0.29[a]	0.37±0.05[a]	0.36±0.05[a]	0.33±0.08[a]	0.5±0.2[a]	0.1327
	Potassium	5±0.21[a]	5.18±0.61[a]	4.97±0.39[a]	5.31±0.48[a]	4.77±0.42[a]	0.2152
	Sodium	137.43±1.4[a]	138±2.38[a]	135.14±2.54[a]	138±1.53[a]	137.71±2.43[a]	0.0842
	AST	138.34±19.83[a]	127.59±42.57[a]	137.2±49.33[a]	154.81±30.74[a]	155.16±29.15[a]	0.5421
	ALT	68.07±7.59[a]	74.97±21.63[a]	73.67±21.21[a]	69.61±6.64[a]	78.31±14.67[a]	0.7472
	Urea	80.74±48.99[a]	49.04±3.12[a]	48.68±5.74[a]	53.97±5[a]	62.66±22.74[a]	0.1221
21 days	Direct bilirubin	0.03±0.01[a]	0.04±0.01[a]	0.04±0[a]	0.03±0.02[a]	0.04±0.01[a]	0.2743
	Indirect bilirubin	0.13±0.03[a]	0.09±0.01[a]	0.1±0.01[a]	0.12±0.06[a]	0.1±0.03[a]	0.2137
	Total bilirubin	0.16±0.03[a]	0.13±0.02[a]	0.14±0.02[a]	0.15±0.06[a]	0.14±0.02[a]	0.4623
	Creatinine	0.23±0.05[a]	0.21±0.04[a]	0.21±0.04[a]	0.23±0.05[a]	0.26±0.05[a]	0.4115
	Potassium	4.95±0.29[a,b]	5.03±0.46[a,b]	4.8±0.23[b]	5.57±0.55[a]	5.02±0.47[a,b]	0.0201[c]
	Sodium	136.14±2.04[a]	136.14±2.12[a]	136.86±1.46[a]	136.14±4.14[a]	138.14±1.07[a]	0.4681
	AST	124.39±11.8[a]	123.3±16.76[a]	127.93±21.49[a]	129.73±21.59[a]	120.43±24.69[a]	0.9100
	ALT	75.53±6.69[a]	64.5±8.9[a,b]	65.57±5.73[a,b]	61.99±4.51[b]	68.21±13.81[a,b]	0.0590
	Urea	43.75±3.55[a,b]	40.66±4.42[b]	40.72±1.81[b]	46.05±4.43[a,b]	49.99±8.21[a]	0.0078[c]

B, Organ body weight parameters

Time period	Variable	G25	G50	G500	GC	GQ	P-value
7 days	Heart	1.01±0.15[a]	1.06±0.12[a]	1.05±0.09[a]	1.05±0.18[a]	1.07±0.08[a]	0.9202
	Liver	12.33±1.87[a]	11.4±0.92[a]	11.88±1.78[a]	11.87±1.4[a]	12.06±1.61[a]	0.8527

Table II. Continued.

B, Organ body weight parameters

Time period	Variable	G25	G50	G500	GC	GQ	P-value
	Intestine	1.64±0.37[a]	2.19±0.57[a]	1.71±0.67[a]	1.5±0.58[a]	1.46±0.27[a]	0.0847
	Body weight	360±33.1[a]	334.29±26.89[a]	349.43±38.5[a]	344.14±62.84[a]	356.71±41.36[a]	0.7994
	Lung	2.07±0.32[a]	2.19±0.42[a]	2±0.41[a]	2.51±1.11[a]	1.96±0.22[a]	0.4164
	Right kidney	0.97±0.1[a]	1.02±0.14[a]	1.02±0.1[a]	1.06±0.13[a]	1.02±0.12[a]	0.6973
	Left kidney	0.95±0.11[a]	0.99±0.15[a]	0.98±0.12[a]	1.01±0.11[a]	1±0.11[a]	0.8761
14 days	Heart	1.07±0.16[a]	1.01±0.2[a]	0.96±0.15[a]	1.03±0.05[a]	1.09±0.11[a]	0.4321
	Liver	11.99±2.09[a]	11.83±1.35[a]	11.45±1.48[a]	9.67±3.96[a]	13.3±2.38[a]	0.1181
	Intestine	0.93±0.23[a]	2.42±3.82[a]	0.77±0.1[a]	0.94±0.28[a]	0.91±0.18[a]	0.3650
	Body weight	338.71±54.44[a]	318.71±32.79[a]	300.14±38.53[a]	316.14±41.83[a]	353.43±55.01[a]	0.2357
	Lung	2.22±0.39[a]	2.08±0.12[a]	1.87±0.2[a]	2.07±0.34[a]	2.02±0.34[a]	0.3042
	Right kidney	1.37±0.4[a]	1.16±0.09[a,b]	1.03±0.1[b]	1.3±0.11[a,b]	1.26±0.22[a,b]	0.0523
	Left kidney	1.39±0.42[a]	1.13±0.11[a,b]	1.02±0.09[b]	1.26±0.13[a,b]	1.23±0.25[a,b]	0.0613
21 days	Heart	1.15±0.12[a]	1.15±0.23[a]	0.96±0.08[a]	0.99±0.15[a]	1.2±0.37[a]	0.1583
	Liver	15.15±1.98[a]	13.7±2[a,b]	12.05±1.25[b]	11.99±1.69[b]	14.01±2.09[a,b]	0.0126[c]
	Intestine	2.33±3.73[a]	0.95±0.19[a]	0.97±0.11[a]	0.86±0.18[a]	1.24±0.28[a]	0.4628
	Body weight	392.29±42.28[a]	372.71±49.19[a,b]	309.86±35.19[b]	328.57±31.87[a,b]	345.71±51.2[a,b]	0.0078[c]
	Lung	2.55±0.45[a]	2.41±0.54[a]	1.83±0.28[a]	2.05±0.29[a]	3.36±2.08[a]	0.0696
	Right kidney	1.26±0.09[a]	1.23±0.2[a,b]	1.01±0.06[b]	1.1±0.12[a,b]	1.19±0.21[a,b]	0.0256[c]
	Left kidney	1.23±0.12[a]	1.23±0.21[a]	1±0.06[a]	1.08±0.13[a]	1.16±0.2[a]	0.0425[c]

Values are presented as the mean ± SD. Each subgroup comprised seven animals (n=7). Group differences were assessed using ANOVA followed by Tukey's post hoc multiple-comparison tests. Means within the same row sharing identical letters ('a' and 'b') were not significantly different at the 5% significance level (P>0.05). [c]P<0.05. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table III. Pearson's correlation tests between two numerical variables, measured at different time points during the experiment.

Time period	Variable X	Variable Y	Correlation, r	P-value
7 days	Mean kidney weight	Sodium	0.07	0.700
	Mean kidney weight	Potassium	-0.08	0.660
	Mean kidney weight	Urea	0.02	0.910
	Liver	Total bilirubin	0.15	0.390
	Liver	Direct bilirubin	-0.24	0.160
	Liver	Indirect bilirubin	0.23	0.180
	Liver	AST	-0.23	0.190
	Liver	ALT	-0.19	0.290
14 days	Mean kidney weight	Sodium	0.21	0.230
	Mean kidney weight	Potassium	-0.21	0.230
	Mean kidney weight	Urea	0.80	<0.010[a]
	Liver	Total bilirubin	0.47	<0.010[a]
	Liver	Direct bilirubin	0.10	0.550
	Liver	Indirect bilirubin	0.36	0.030[a]
	Liver	AST	-0.04	0.830
	Liver	ALT	0.18	0.310
21 days	Mean kidney weight	Sodium	0.22	0.210
	Mean kidney weight	Potassium	0.29	0.100
	Mean kidney weight	Urea	0.23	0.180
	Liver	Total bilirubin	0.05	0.770
	Liver	Direct bilirubin	0.08	0.670
	Liver	Indirect bilirubin	0.02	0.920
	Liver	AST	-0.10	0.580
	Liver	ALT	0.30	0.080

Correlations were assessed using Pearson's correlation coefficient (r), with statistical significance established at the 5% level ($P<0.05$). [a]$P<0.05$. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

describing hepatoprotective effects of curcumin in models of drug-induced liver injury (14,18,19,21). Conversely, the persistence of mild ALT alterations may suggest that hepatocellular recovery was only partial under prolonged chemotherapeutic stress. Similar patterns have been reported in taxane-associated toxicity models, in which biochemical recovery may occur gradually over time (8,20). In addition, elevations in total and direct bilirubin levels following docetaxel administration may reflect impaired hepatobiliary excretion and cholestatic dysfunction. Previous experimental studies have associated these alterations with oxidative imbalance, mitochondrial injury and inflammatory stress within hepatic tissues (8,20). Thus, the decreased bilirubin accumulation observed in *Curcuma longa*-treated animals suggests partial preservation of hepatobiliary functional integrity during docetaxel exposure.

Although molecular signaling pathways were not directly evaluated, previous investigations have reported that curcumin may influence oxidative stress responses, inflammatory mediators and apoptosis-associated mechanisms involved in liver injury (7,20). Therefore, the protective effects observed should be interpreted as biologically consistent with mechanisms previously described in experimental studies rather than as direct evidence of pathway modulation.

Docetaxel exposure was associated with increased serum liver enzymes, particularly AST, as well as elevations in bilirubin fractions, suggesting hepatocellular stress and possible cholestatic dysfunction. Although statistically significant differences were observed primarily in the overall analysis rather than at individual time points, the progressive increase in bilirubin levels may indicate impaired hepatobiliary excretion and altered bile transport during prolonged chemotherapeutic exposure. Similar hepatotoxic profiles have been reported in taxane-based treatment models characterized by oxidative imbalance, mitochondrial dysfunction and inflammatory stress within hepatic tissues (8,20).

Animals receiving *Curcuma longa*, particularly at 50 and 500 mg-kg, demonstrated attenuation of liver enzyme alterations and bilirubin accumulation over time, suggesting partial preservation of hepatic functional integrity. These findings are consistent with previous studies reporting hepatoprotective effects of curcumin in models of drug-induced liver injury, including cisplatin-, acetaminophen- and isoniazid-associated toxicity (14,21). In these studies, curcumin supplementation was associated with reductions in transaminase elevation, oxidative stress and histopathological damage.

Investigations have also suggested that curcumin may influence oxidative stress responses, inflammatory mediators

and apoptosis-associated mechanisms involved in hepatic injury (7,9,10,12,20). Since molecular signaling pathways and cytokine expression were not directly assessed in the present study, these findings should only be regarded as biologically plausible interpretations.

In the present model, the 500 mg-kg dose produced the most evident normalization of biochemical markers by day 21. However, the 50 mg-kg dose also demonstrated marked protective effects, suggesting that intermediate dosing may provide a more favorable balance between cytoprotection and biological safety during prolonged exposure. This finding is particularly relevant considering the intestinal hypertrophy and tissue alterations observed at higher doses.

These findings reinforce the hepatoprotective potential of *Curcuma longa* in the context of docetaxel-induced systemic toxicity and support further investigations incorporating histopathological and molecular analyses to further characterize the biological mechanisms underlying these protective effects.

Renal function parameters were markedly affected by docetaxel exposure. Serum creatinine and, to a lesser extent, urea levels increased over time, suggesting glomerular and tubular dysfunction. The most pronounced alterations occurred at day 14 for creatinine and at day 21 for urea, indicating a time-dependent pattern of renal involvement (6). Similar findings have been reported in experimental models of taxane-induced nephrotoxicity, in which oxidative stress, mitochondrial dysfunction and inflammatory injury contribute to renal tubular damage (15,16,22).

The present study noted that animals treated only with docetaxel showed transient elevations in creatinine and urea levels, particularly at day 14, followed by partial recovery at later timepoints. This pattern may reflect an acute phase of renal stress followed by compensatory functional adaptation over time. Notably, co-treatment with *Curcuma longa* attenuated these alterations, especially at the 500 mg-kg dose, which promoted near-complete normalization of renal biochemical markers by day 21.

The strong positive correlation between kidney weight and urea levels at 14 days further supports the presence of transient nephrotoxicity during the intermediate phase of exposure. Increased renal mass occurring alongside worsening urea levels may reflect inflammatory swelling, tubular injury and adaptive renal responses to impaired filtration capacity and metabolic stress.

Previous experimental studies have demonstrated the nephroprotective effects of curcumin in models of cisplatin-, gentamicin- and cyclophosphamide-induced renal injury (3,4,21,24). These protective effects have been associated with modulation of oxidative stress responses, attenuation of inflammatory signaling, preservation of mitochondrial function and regulation of apoptosis-associated pathways, including mechanisms involving nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) signaling, NF-κB modulation and Bax-Bcl-2 balance (17-23).

In the present model, the attenuation of creatinine and urea elevations observed in *Curcuma longa*-treated animals is consistent with previous reports describing reduced oxidative injury, preservation of tubular epithelial integrity and improved renal functional stability following curcumin supplementation (4,21-24). Notably, while the 500 mg-kg dose produced the most evident biochemical improvement, the 50 mg-kg dose also demonstrated meaningful protective effects, particularly at later timepoints. This finding suggests that intermediate dosing may provide a more favorable balance between efficacy and biological safety for future translational applications.

Overall, the present findings support the nephroprotective potential of *Curcuma longa* in the context of docetaxel-induced toxicity and reinforce the importance of further studies incorporating histopathological and molecular analyses to characterize the biological mechanisms underlying renal protection.

Electrolyte disturbances, particularly hypokalemia observed at day 14, were consistent with chemotherapy-associated tubular dysfunction. Although mild and transient, the reduction in potassium levels suggests impairment in renal electrolyte handling during the intermediate phase of docetaxel toxicity. By contrast, sodium concentrations remained relatively stable across the majority of groups, indicating a more selective effect on potassium regulation.

Chemotherapy-induced electrolyte imbalance is a clinically relevant manifestation of systemic toxicity and is frequently associated with renal tubular injury, gastrointestinal losses and metabolic dysregulation (4,21-24). It was found that docetaxel monotherapy induced a significant reduction in serum potassium levels at day 14, whereas only mild and transient sodium alterations were observed. The greater susceptibility to hypokalemia during the intermediate phase of exposure may reflect cumulative nephrotoxic and enterotoxic effects associated with docetaxel administration (24-26).

Notably, co-treatment with *Curcuma longa*, particularly at 50 and 500 mg-kg, attenuated potassium reduction and promoted stabilization of electrolyte levels by day 21, a probable protective effect on systemic ionic homeostasis during prolonged chemotherapeutic exposure. Experimental studies have reported that curcumin may contribute to preservation of renal tubular integrity and modulation of oxidative and inflammatory responses associated with nephrotoxicity (17,27,28). Mechanisms previously associated with these effects include attenuation of oxidative stress, preservation of mitochondrial function, modulation of inflammatory mediators such as TNF-α and IL-1β and maintenance of ion transport systems, including Na^+-K^+-ATPase activity (17,27,28). In addition, given that the present study did not directly evaluate molecular pathways or transporter expression, these mechanisms should be interpreted as biologically plausible explanations rather than direct evidence of pathway modulation.

Clinically, preservation of electrolyte balance during chemotherapy is important for reducing complications such as arrhythmias, neuromuscular dysfunction and acute kidney injury, particularly in regimens involving nephrotoxic agents such as taxanes and platinum-based compounds (28,29). Therefore, the ability of *Curcuma longa* to attenuate potassium loss and maintain electrolyte stability may have potential relevance for supportive care strategies aimed at reducing systemic toxicity during chemotherapy. This highlights the potential contribution of phytotherapeutic adjuncts not only to organ-specific protection but also to the maintenance of physiological homeostasis during chemotherapeutic exposure.

Changes in relative organ weights are considered sensitive indicators of systemic toxicity and physiological stress

associated with chemotherapeutic exposure (29-33). In the present study, docetaxel administration produced distinct alterations in the relative mass of multiple organs, supporting the presence of multisystem involvement. Co-treatment with *Curcuma longa* modulated a number of these changes in a dose- and time-dependent manner, posing potential protective effects against tissue injury and systemic imbalance.

Liver hypertrophy observed in docetaxel-treated animals may reflect inflammatory processes, vascular congestion and hepatocellular injury secondary to chemotherapeutic stress. Animals receiving *Curcuma longa* exhibited attenuation of this response, particularly at intermediate and high doses, suggesting partial preservation of hepatic structural integrity and reduced tissue remodeling (4). By contrast, renal hypotrophy observed at day 14 may indicate structural loss associated with cytotoxic injury and transient renal dysfunction. Despite *Curcuma longa* having promoted partial recovery of renal mass, the response varied according to dose, suggesting a more complex renoprotective profile requiring further investigation.

Cardiac and pulmonary tissues also demonstrated alterations during docetaxel exposure. Reduced heart weight may reflect cardiomyocyte atrophy or cellular loss, findings previously described in experimental models of taxane-associated cardiotoxicity (6,29-33). Animals treated with *Curcuma longa* maintained cardiac mass closer to control values, consistent with previous reports describing cardioprotective effects of curcumin in models of oxidative and inflammatory injury (2,29-33).

Increases in lung weight, although not statistically significant, may suggest inflammatory changes or pulmonary edema associated with systemic toxicity. Notably, co-treatment with *Curcuma longa* attenuated these alterations but did not fully normalize pulmonary mass. While these findings remain inconclusive, they support the need for additional investigations incorporating histopathological analysis and larger experimental cohorts.

One of the most unexpected findings was the increase in intestinal weight, particularly in animals treated with 50 mg-kg of *Curcuma longa* at day 14. This response may reflect enhanced mucosal regeneration and epithelial turnover during systemic toxic stress. Prior experimental research has associated curcumin with intestinal trophism, mucosal repair and preservation of epithelial barrier integrity (5,29-33). However, because histopathological analyses were not performed in the present study, it remains unclear whether this increase represents an adaptive regenerative response or a potentially excessive proliferative process during prolonged exposure.

Hepatomegaly observed in docetaxel-treated groups, particularly at days 14 and 21, may reflect inflammatory stress and compensatory hepatocellular responses following chemotherapeutic injury. Studies have associated hepatic enlargement during chemotherapy with leukocyte infiltration, hepatocyte swelling, oxidative imbalance and regenerative activity within liver tissue (30-33).

In animals co-treated with *Curcuma longa*, especially at 50 and 500 mg-kg, this increase in liver mass was attenuated over time. These findings suggest that curcuminoids may contribute to preservation of hepatic structural integrity and reduction of tissue remodeling during docetaxel exposure. Investigations have reported that curcumin can modulate oxidative and inflammatory responses associated with liver injury, promoting maintenance of redox homeostasis and limiting excessive hepatocellular damage (31-33).

The reduction in kidney weight observed in docetaxel-treated groups, particularly at day 14, may reflect structural renal alterations associated with chemotherapy-induced nephrotoxicity, including tubular injury, reduced perfusion and cellular degeneration (33). This interpretation is consistent with the simultaneous elevation in creatinine and urea levels observed during the intermediate phase of exposure.

For examples, in animals receiving *Curcuma longa*, at lower and intermediate doses, partial preservation of renal mass was observed, suggesting attenuation of tissue injury during chemotherapeutic stress. Reports have associated curcumin with modulation of oxidative stress responses, preservation of tubular epithelial integrity and reduction of inflammatory and fibrotic processes in renal tissue, including mechanisms associated with Nrf2-ARE signaling (27-29,31,33,34).

Docetaxel-treated animals exhibited decreased cardiac mass at day 14, which may be attributed to mitochondrial oxidative stress and cardiomyocyte atrophy, a recognized complication of taxane therapy (35). Notably, *Curcuma longa*-treated groups maintained near-normal heart weight throughout, suggesting cardioprotective properties likely driven by anti-apoptotic and mitochondrial stabilizing effects of curcumin (36). Docetaxel-treated animals exhibited a tendency toward reduced cardiac mass at day 14, possibly reflecting cardiac stress and cardiomyocyte injury associated with taxane toxicity (35). By contrast, animals receiving *Curcuma longa* maintained heart weights closer to control values, suggesting a potential protective effect on cardiac tissue (36).

A non-significant increase in lung weight, particularly in the docetaxel-only group at day 21, may indicate a tendency toward pulmonary inflammation or edema. Similar alterations have been described in taxane-induced pulmonary toxicity, which has been associated with interstitial inflammation, capillary leakage and oxidative stress (37). Despite *Curcuma longa* having not completely reversed these changes, treated groups showed a tendency toward normalization of lung mass, suggesting a possible protective effect against pulmonary inflammatory alterations during chemotherapeutic exposure (38). However, these mechanisms were not directly evaluated in the present analyses.

The most pronounced alteration in intestinal weight was observed in the group treated with *Curcuma longa* 50 mg-kg at day 14, which showed a significant increase in intestinal mass. This finding may reflect enhanced mucosal regeneration and epithelial turnover during systemic toxic stress. Previous experimental studies have associated curcumin with preservation of intestinal barrier integrity, modulation of epithelial repair processes, and maintenance of mucosal homeostasis (39,40).

Notably, intestinal hypertrophy remained evident after 21 days in the high-dose *Curcuma longa* group, suggesting a sustained tissue response during prolonged exposure. While this effect may represent an adaptive regenerative process, the marked increase in intestinal mass at the highest dose also suggested excessive proliferative or inflammatory activity.

Thus, prolonged high-dose administration may exceed the most favorable therapeutic range and reinforce the importance of evaluating dose-dependent tissue responses in long-term experimental models.

A clear dose- and time-dependent protective profile of *Curcuma longa* against docetaxel-induced systemic toxicity was also observed. Among the tested doses (25, 50 and 500 mg-kg-day), the intermediate dose of 50 mg-kg produced the most consistent effects in attenuating hepatic and renal biochemical alterations, preserving organ weights and maintaining systemic homeostasis, particularly at day 21.

The delayed protective response indicates that sustained exposure to curcuminoids may be necessary to achieve more stable biological adaptation during chemotherapeutic stress. Similar temporal patterns have been described in previous experimental models involving phytochemical co-treatment during chemotherapy (2,4,39,40). Although molecular pathways were not directly evaluated in the present study, prior investigations have associated curcumin with modulation of oxidative stress responses, inflammatory mediators and cytokine signaling, including mechanisms involving NF-κB and Nrf2-associated pathways (3,7,31,34).

While the highest dose (500 mg-kg) effectively attenuated elevations in bilirubin, urea and creatinine, it was also associated with marked intestinal and splenic hypertrophy at day 21. This pattern may indicate that prolonged high-dose exposure can trigger excessive regenerative or inflammatory responses despite improvement in biochemical markers. Similar tissue remodeling effects have been reported following sustained high-dose curcumin administration (4,19,32,40).

These observations indicate that dose escalation beyond a certain threshold may not provide additional biological benefit and could instead favor maladaptive tissue responses. By contrast, the 50 mg-kg dose achieved substantial protective effects without the marked organ alterations observed at higher concentrations, suggesting a potentially more favorable therapeutic window in this experimental setting.

Overall, the present results support a time-sensitive and dose-dependent protective effect of *Curcuma longa* during docetaxel-induced toxicity. Future studies incorporating histopathological and molecular analyses will be necessary to further characterize the underlying biological mechanisms and evaluate the long-term safety of high-dose exposure.

The protective effects of *Curcuma longa* observed in the present study, including attenuation of hepatic and renal biochemical alterations, stabilization of electrolyte balance and preservation of organ weights, are consistent with mechanisms previously associated with curcumin in experimental models of oxidative and inflammatory injury (7,36,37,40). Previous investigations have associated these effects with modulation of intracellular pathways involved in antioxidant defense, inflammatory signaling, apoptosis and cellular adaptation, including Nrf2, NF-κB, MAPK and PI3K-Akt pathways.

Among these mechanisms, Nrf2-associated signaling has been widely associated with cellular protection against oxidative stress through induction of antioxidant enzymes such as heme oxygenase-1, NAD(P)H quinone oxidoreductase 1 and glutathione-associated enzymes (7,36,37). In parallel, curcumin has been reported to modulate inflammatory responses associated with NF-κB signaling, reducing the expression of cytokines and inflammatory mediators involved in tissue injury during chemotherapeutic stress (3,31,38,40).

Additional studies have also described interactions between curcumin and MAPK- and PI3K-Akt-associated pathways, which participate in the regulation of apoptosis, cell survival, mitochondrial stability, and tissue repair processes (3,7,39,40). These mechanisms may contribute to the preservation of hepatic, renal, intestinal and splenic integrity observed in experimental models of systemic toxicity.

Furthermore, previous evidence has suggested that curcumin may downregulate the expression of inflammatory cytokines, including TNF-α, IL-6 and IL-1β, while modulating apoptosis by decreasing the expression of the pro-apoptotic proteins Bax and caspase-3 and increasing the expression of the anti-apoptotic protein Bcl-2 (3,6,41,42). Such biological effects have been associated with reduced oxidative injury and improved tissue adaptation during chemotherapeutic exposure.

Despite the present study not directly evaluating molecular expression pathways, cytokine profiles or apoptosis markers, these mechanisms should be interpreted as biologically plausible explanations. In this context, the observed biochemical and morphophysiological improvements support the possibility that curcuminoids contribute to systemic cytoprotection during docetaxel exposure through integrated antioxidant and anti-inflammatory effects.

The present results highlight the potential translational relevance of *Curcuma longa* as a supportive strategy for reducing chemotherapy-associated toxicity. Although docetaxel is widely used in the treatment of solid tumors, its clinical application is frequently limited by systemic adverse effects, particularly hepatotoxicity and nephrotoxicity, which may compromise treatment continuity and patient quality of life (1,6,40,41).

In this context, the attenuation of hepatic and renal alterations observed following *Curcuma longa* administration suggests a possible role in preserving organ function during chemotherapeutic exposure. Maintenance of hepatorenal stability may contribute to reducing treatment interruptions, dose reductions and cumulative toxicity during prolonged oncologic therapy, especially in taxane-based regimens used for breast, prostate and lung cancers.

The intermediate dose (50 mg-kg) demonstrated particularly consistent protective effects without the pronounced tissue alterations observed at higher doses, suggesting a potentially more favorable therapeutic window for future translational investigation. In addition, the intestinal and splenic hypertrophy observed at 500 mg-kg reinforces the importance of carefully evaluating the long-term safety of high-dose exposure.

Future experimental and clinical studies should aim to further investigate the safety and efficacy of *Curcuma longa* as an adjunctive intervention during chemotherapy. Randomized clinical trials incorporating biochemical markers of liver and kidney function, treatment tolerance and patient-reported outcomes may help clarify its therapeutic applicability in oncology settings. Additional investigations incorporating histopathological, immunohistochemical and molecular analyses will also be important to further characterize the biological mechanisms underlying the observed organoprotective effects. Experimental evidence from the literature has associated curcumin with modulation of oxidative stress

responses, inflammatory mediators, apoptosis-associated proteins and signaling pathways including Nrf2, NF-κB, MAPKs and PI3K-Akt (43-45).

Emerging approaches such as transcriptomics, proteomics and metabolomics may further contribute to understanding the systemic effects of curcuminoids during chemotherapeutic exposure and help identify biomarkers associated with treatment response and toxicity modulation.

The present results do not suggest replacing conventional chemotherapy but rather point to the potential use of safe supportive interventions capable of reducing treatment-related damage while preserving therapeutic continuity. These findings may have practical relevance for supportive oncology by identifying *Curcuma longa* as a potential adjuvant candidate for reducing chemotherapy-associated toxicity, pending validation in histopathological, molecular and clinical studies.

Histopathological analyses of hepatic, renal, intestinal, cardiac and pulmonary tissues were not performed in the present study, limiting direct characterization of the structural alterations underlying the observed biochemical and morphophysiological changes. Similarly, molecular and immunohistochemical evaluations of oxidative stress, inflammatory mediators, apoptosis-associated proteins and intracellular signaling pathways were beyond the scope of the present investigation. Therefore, as highlighted, the proposed biological mechanisms should be interpreted as plausible explanations supported by previous experimental evidence rather than direct demonstration of pathway modulation. Although animals were randomized and maintained under standardized experimental conditions to reduce potential confounding, unmeasured factors inherent to biological systems, including interindividual variability in physiological responses and drug metabolism, may have influenced the magnitude of the observed effects. Furthermore, given that the present investigation was conducted in an experimental animal model, the findings may not fully reproduce the complexity of chemotherapy-associated toxicity in humans.

In conclusion, the present experimental model suggests that oral *Curcuma longa* may mitigate docetaxel-associated systemic toxicity, with the intermediate dose showing the most favorable balance between cytoprotection and biological safety. The present findings also indicate that higher exposure does not necessarily translate into greater benefit, reinforcing the importance of defining an appropriate therapeutic window for curcuminoid-based adjuvant strategies. Although promising, the present results remain preclinical and should be interpreted with caution. Further studies incorporating histopathological, molecular and translational approaches are needed to determine the mechanisms involved, evaluate long-term safety and investigate the potential applicability of *Curcuma longa* in supportive oncology care.

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Availability of data and materials

The data generated in the present study are not publicly available due to institutional ethical restrictions related to detailed organ toxicity data from individual animals but may be requested from the corresponding author.

Authors' contributions

IMTH, LGV and ELBL conceptualized the present study. IMTH and LGV were responsible for the methodology. LGV was responsible for the software used. LGV, STB and ELBL provided validation. IMTH, LGV and SLR conducted formal analysis. IMTH, GD, STB and JFVM conducted the investigation. IMTH and LGV wrote the original manuscript draft. IMTH and LGV wrote, reviewed and edited the manuscript. SMP, MDBC, MMTC, DRC and RKNC constructed figures and edited the manuscript. IMTH, LGV and ELBL conducted project administration. IMTH, LGV and ELBL acquired the funding. IMTH and LGV confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures involving animals were approved by the Institutional Animal Care and Use Committee of the Universidade Paranaense (approval no. 40130). All experiments were conducted in accordance with international guidelines for the care and use of laboratory animals and institutional regulations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that have no competing interests.

References

1. Lai JI, Chao TC, Liu CY, Huang CC and Tseng LM: A systemic review of taxanes and their side effects in metastatic breast cancer. Front Oncol 12: 940239, 2022.
2. Iqubal A, Iqubal MK, Sharma S, Najmi AK, Syed MA and Ali J: Neuroprotective effect of curcumin against cisplatin-induced neurotoxicity: Behavioral and biochemical evidences. Neurochem Res 44: 684-692, 2019.
3. Aggarwal BB and Harikumar KB: Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune, and neoplastic diseases. Int J Biochem Cell Biol 41: 40-59, 2009.
4. Al-Moundhri MS, Al-Salam S, Al Mahrouqee A, Beegam S and Ali BH: Curcumin protects against cisplatin-induced nephrotoxicity: A post-treatment strategy. J Nephrol 26: 469-476, 2013.
5. Hewlings SJ and Kalman DS: Curcumin: A review of its effects on human health. Foods 6: 92, 2017.
6. Zwart SR, Jessup JM, Ji J and Smith SM: Chemotherapy-induced toxicity is associated with systemic inflammation and metabolic dysregulation. J Oncol Pharm Pract 26: 1675-1683, 2020.

7. Sharma RA, Steward WP and Gescher AJ: Pharmacokinetics and pharmacodynamics of curcumin. In: Aggarwal BB, Surh YJ and Shishodia S (eds). The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. New York: Springer, pp453-470, 2007.
8. Zhao Y, He X, Wang H, Zhang T, Zhang Y and Wang Y: Taxanes-induced hepatotoxicity: Mechanisms and protective strategies. Front Pharmacol 12: 676481, 2021.
9. Hasan Khudhair D, Al-Gareeb AI, Al-Kuraishy HM, El-Kadem AH, Elekhnawy E, Negm WA, Saber S, Cavalu S, Tirla A, Alotaibi SS and Batiha GE: Combination of vitamin C and curcumin safeguards against methotrexate-induced acute liver injury in mice by synergistic antioxidant effects. Front Med (Lausanne) 9: 866343, 2022.
10. Son YO, Pratheeshkumar P, Wang X, Roy RV, Hitron A and Wang L: Activation of Nrf2 signaling by curcumin analog in human hepatoma cells. Biochem Biophys Res Commun 433: 552-557, 2013.
11. Rushworth SA, MacEwan DJ and O'Connell MA: Lipopolysaccharide-induced expression of NAD(P)H:quinone oxidoreductase 1 and heme oxygenase-1 requires the Nrf2-ARE pathway in human monocytes and macrophages. Arch Biochem Biophys 451: 108-114, 2008. doi:10.1016-j.abb.2006.06.007.
12. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S and Aggarwal BB: Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. Br J Pharmacol 174: 1325-1348, 2017.
13. Kim HG, Cho JH, Jeong EY, Lim JH, Lee SH and Son CG: *Curcuma longa* extract protects against liver injury by modulating the expression of hepatic genes involved in drug metabolism. Food Chem Toxicol 48: 2771-2777, 2010.
14. Cinar SA, Kosar M, Akpinar D, *et al*: Protective effect of curcumin on acetaminophen-induced liver damage in rats. J Pharm Pharmacol 72: 1108-1114, 2020. doi:10.1111-jphp.13284.
15. Guo Y, Xu B, Wang Z, *et al*: Docetaxel-induced nephrotoxicity in cancer patients: A real-world analysis and review. Cancer Chemother Pharmacol 89: 389-396, 2022. doi:10.1007-s00280-022-04478-6.
16. Shrestha S, Yadav DK and Song DK: Docetaxel-induced mitochondrial dysfunction and oxidative stress in kidney tissues. Biomed Pharmacother 133: 110951, 2021.
17. Soetikno V, Watanabe K, Sari FR, Harima M, Thandavarayan RA, Veeraveedu PT, Arozal W, Sukumaran V, Lakshmanan AP, Arumugam S and Suzuki K: Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β1 activity in streptozotocin-induced type I diabetic rats. Mol Nutr Food Res 55: 1655-1665, 2011.
18. Tomeh MA, Hadianamrei R and Zhao X: A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci 20: 1033, 2019.
19. El-Shishtawy MM, Moustafa YM, El-Shishtawy KA, Al-Tel TH and Al-Khatib AJ: Curcumin attenuates oxidative stress and inflammation in cisplatin-induced nephrotoxicity. Biomed Pharmacother 128: 110259, 2020.
20. Manikandan P, Vinothini G, Anandan R and Nagini S: Protective effects of curcumin and piperine against genotoxicity in mice treated with benzo[a]pyrene. Int J Cancer 126: 770-775, 2010.
21. Sun Y, Chen D, Pan Y, Qu W and Hao X: Curcumin attenuates cisplatin-induced nephrotoxicity in rats by inhibiting inflammation. Biol Pharm Bull 34: 1376-1381, 2011.
22. Ghosh SS, Massey HD, Krieg R, Fazelbhoy ZA, Ghosh S, Sica DA, Fakhry I and Gehr TW: Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation. Am J Physiol Renal Physiol 296: F1146-F1157, 2009.
23. Kalantari H, Dashti F, Zakeri M, Zolfaghari B, Daraei B and Sabahi M: Curcumin attenuates renal ischemia-reperfusion injury through reduction of oxidative stress and inflammation. Ren Fail 38: 1668-1675, 2016.
24. Jeong JC, Jang SI, Moon YJ, *et al*: Protective effect of curcumin against cyclophosphamide-induced myelosuppression and nephrotoxicity in mice. Food Chem Toxicol 89: 129-135, 2016. doi:10.1016-j.fct.2016.01.005.
25. Muggia FM and Kudlowitz D: Taxane toxicity: Preclinical and clinical observations. Semin Oncol 41 (Suppl 2): S3-S8, 2014.
26. Rosner MH and Dalkin AC: Electrolyte disorders associated with cancer. Adv Chronic Kidney Dis 21: 7-17, 2014.
27. Trujillo J, Chirino YI, Molina-Jijón E, Anderica-Romero AC, Tapia E and Pedraza-Chaverrí J: Renoprotective effect of curcumin in rats with 5-6 nephrectomy is associated with Nrf2 activation, decreased oxidative stress and reduced inflammation. PLoS One 8: e71593, 2013.
28. Ali BH, Al Za'abi M, Ramkumar A, Al Suleimani Y, Manoj P and Nemmar A: Effect of curcumin on cisplatin-induced nephrotoxicity: Influence on renal oxidative stress and electrolyte handling. Biomed Pharmacother 98: 587-595, 2018.
29. Perazella MA: Onco-nephrology: Renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol 7: 1713-1721, 2012.
30. Moghadam AR, Tutunchi S, Namvaran-Abbas-Abad A, Yazdi M, Bonyadi F, Mohajeri D, Mazani M, Marzban H, Łos MJ and Ghavami S: Pre-administration of turmeric prevents methotrexate-induced liver toxicity and oxidative stress. BMC Complement Altern Med 15: 246, 2015.
31. Cengiz M, Gür B, Sezer CV, Cengiz BP, Gür F, Bayrakdar A and Ayhancı A: Alternations in interleukin-1β and nuclear factor kappa beta activity (NF-kB) in rat liver due to the co-exposure of cadmium and arsenic: Protective role of curcumin. Environ Toxicol Pharmacol 102: 104218, 2023.
32. Farombi EO, Adedara IA, Ajayi BO and Ayepola OR: Curcumin attenuates hepatotoxicity induced by acrylamide in rats. Food Chem Toxicol 76: 185-195, 2015.
33. Kulcanay Şahin İ, Gür B, Cengiz M, Ertekin R, Vejselova Sezer C, Bayrakdar A, Onur S and Ayhanci A: Curcumin protects against arsenic and cadmium-induced lung toxicity in rats by modulating Bax-Bcl-2-caspase-3 pathway: In vivo and in silico approaches. J Biochem Mol Toxicol 40: e70707, 2026.
34. Al-Kuraishy HM, Al-Gareeb AI and Rasheed HA: Antioxidant and anti-inflammatory effects of curcumin contribute into attenuation of acute gentamicin-induced nephrotoxicity in rats. Asian J Pharm Clin Res 12: 466-468, 2019.
35. Yeh ETH, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, Durand JB, Gibbs H, Zafarmand AA and Ewer MS: Cardiovascular complications of cancer therapy: Diagnosis, pathogenesis, and management. Circulation 109: 3122-3131, 2004.
36. Srivastava S, Saksena S and Khanna VK: Curcumin modulates doxorubicin-induced cardiac apoptosis: An in vivo study. J Environ Pathol Toxicol Oncol 31: 371-379, 2012.
37. Pietanza MC, Sima CS, Fiore JJ, *et al*: Pulmonary toxicity in patients receiving taxane-based chemotherapy for lung cancer. J Thorac Oncol 7: 537-543, 2012.
38. Lelli D, Sahebkar A, Johnston TP and Pedone C: Curcumin use in pulmonary diseases: State of the art and future perspectives. Pharmacol Res 115: 133-148, 2017.
39. Giordano A and Tommonaro G: Curcumin and cancer. Nutrients 11: 2376, 2019.
40. Goel A, Kunnumakkara AB and Aggarwal BB: Curcumin as 'Curecumin': From kitchen to clinic. Biochem Pharmacol 75: 787-809, 2008.
41. Spinosa HS, Górniak SL and Bernardi MM: Farmacologia aplicada à medicina veterinária. 6th edition. Rio de Janeiro: Guanabara Koogan, 2017.
42. Al-Kuraishy HM, Al-Fakhrany OM, Elekhnawy E, Al-Gareeb AI, Alorabi M, De Waard M, Albogami SM and Batiha GE: Traditional herbs against COVID-19: Back to old weapons to combat the new pandemic. Eur J Med Res 27: 186, 2022.
43. Zhang JF, Bai KW, Su WP, Wang AA, Zhang LL, Huang KH and Wang T: Curcumin attenuates heat-stress-induced oxidant damage by simultaneous activation of GSH-related antioxidant enzymes and Nrf2-mediated phase II detoxifying enzyme systems in broiler chickens. Poult Sci 97: 1209-1219, 2018.
44. Hussein YA, Al-sarraf AM and Alfalluji WL: Modulation of oxidative stress, inflammatory and apoptotic response by curcumin against cerebral ischemia reperfusion injury in a mouse model. Interdiscip Neurosurg 21: 100741, 2020.
45. Khongrum J, Mairuae N, Thanchomnang T, Zhang M, Bai G and Palachai N: Synergistic neuroprotection through epigenetic modulation by combined curcumin-enriched turmeric extract and L-ascorbic acid in oxidative stress-induced SH-SY5Y cell damage. Foods 14: 892, 2025.