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Cosmos caudatus Extract Attenuates Doxorubicin-Induced Renal Histopathological Injury in Female Wistar Rats

Febrisma Bangun Sanjaya* , Ahista Saskirana Putri, Gresisce Joice Margaretha Julius, Rizal Muhaimin, Johanes Aprilius Falerio Kristijanto
Universitas Wijaya Kusuma Surabaya, Indonesia
Email: febrizma10@gmail.com* , putriiahistaa@gmail.com, gresiscejoice67@gmail.com, rizalpeka63@gmail.com, jafk114@mhs.uwks.ac.id

ABSTRACT:
Doxorubicin, a widely used anthracycline chemotherapeutic agent, is constrained by dose-limiting nephrotoxicity, which can compromise treatment continuity and patient outcomes. *Cosmos caudatus*, an edible herb rich in polyphenols and flavonoids, possesses documented antioxidant and anti-inflammatory properties, yet its potential to protect against doxorubicin-induced kidney injury remains unexplored. This research aimed to investigate the renoprotective effects of an ethanolic extract of *Cosmos caudatus* (CCE) against doxorubicin-induced renal histopathological damage in a preventive in vivo model. Female Wistar rats (n=5 per group) were allocated into three groups: normal control (NC), doxorubicin-treated (DOX; 5 mg/kg i.p. weekly for 4 weeks), and doxorubicin plus CCE (DOX+CCE; 200 mg/kg/day orally with 1-week pretreatment). Upon completion, left kidneys were processed for histopathological examination using hematoxylin and eosin (H&E) staining. Renal injury was semi-quantitatively assessed across endothelial, glomerular, tubular, and interstitial domains using the EGTI scoring system by a blinded pathologist. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. Doxorubicin administration induced significant histopathological damage across all renal compartments compared to the NC group (all $p < 0.0001$). Co-treatment with CCE significantly attenuated injury severity in each domain (endothelium, $p=0.0071$; glomerulus, $p=0.0240$; tubules, $p=0.0018$; interstitial, $p=0.0004$) and reduced the total EGTI score compared to the DOX group ($p < 0.0001$). However, scores in the DOX+CCE group remained elevated relative to NC, indicating partial protection. Ethanolic extract of *Cosmos caudatus* significantly attenuates doxorubicin-induced renal histopathological injury in female Wistar rats, supporting its potential as a complementary renoprotective agent.

Keywords: Doxorubicin; Nephrotoxicity; Kidney Histopathology; *Cosmos caudatus*.

INTRODUCTION

Cancer continues to impose a major global health burden. In 2022, the world recorded approximately 19.98 million new cancer cases and an estimated 9.74 million deaths, and demographic trends alone are projected to push annual incident cases up to 35 million by 2050 (Bray et al., 2024). This rising burden sustains reliance on established, broadly active chemotherapies. Among these, the anthracycline doxorubicin remains central across multiple malignancies because of its potent antitumor activity, mediated through DNA intercalation, topoisomerase II inhibition, mitochondrial perturbation, and redox cycling (Kciuk et al., 2023; Pugazhendhi et al., 2018).

Clinical benefit, however, is tempered by off-target toxicity. While cardiotoxicity is the best-recognized limitation, kidney injury is increasingly relevant in contemporary oncology because it

can complicate dosing, prolong hospitalization, and restrict subsequent therapy (Lu et al., 2025). Epidemiologically, acute kidney injury (AKI) is not uncommon among patients with cancer: a large analysis of cancer admissions reported an AKI incidence of approximately 11.3%, and pooled evidence in malignant tumor populations has suggested overall AKI rates around one in four, with wide variation by setting and definition (Nazzal et al., 2022). These data underscore why kidney protection is not merely supportive care—it is part of maintaining treatment continuity.

Experimental and translational studies indicate that doxorubicin-induced nephrotoxicity is driven by converging pathways, including excessive reactive oxygen species generation, inflammatory signaling, mitochondrial dysfunction, and downstream cell-death and pro-fibrotic responses, ultimately producing glomerular and tubulointerstitial injury patterns that are readily captured histopathologically (Afsar et al., 2020; Lu et al., 2025). The absence of a routinely implemented, kidney-specific preventive strategy for anthracycline exposure has motivated interest in adjunctive agents that can modulate redox and inflammatory cascades without undermining anticancer efficacy.

Plant-derived polyphenol- and flavonoid-rich preparations are frequently explored in this context because they target central mechanisms implicated in toxic organ injury (Kang et al., 2021). Previous studies have investigated various botanicals for nephroprotection. For example, *Acacia hydaspica* extract demonstrated attenuation of doxorubicin-induced oxidative stress and histopathological damage in rat kidneys (Afsar et al., 2020). Similarly, *Andrographis paniculata* and naringin have shown promising renoprotective effects in similar models by modulating inflammation and oxidative pathways (Arozal et al., 2025; Gad et al., 2025). However, research on edible plants commonly consumed in Southeast Asia remains limited.

Cosmos caudatus, an edible medicinal herb widely consumed in Southeast Asia, has been reported to exhibit substantial antioxidant capacity and diverse bioactivities (Ahda et al., 2023). Modern profiling studies, including metabolomics analysis, further support that *C. caudatus* extracts contain appreciable phenolic and flavonoid constituents alongside measurable antioxidant activity (Rafi et al., 2023; Wan-Nadilah et al., 2019). Previous research has documented its health benefits, such as improving bone metabolism markers in rats (Sari et al., 2024) and cognitive function in older adults (You et al., 2021), but its specific role in chemotherapy-induced nephrotoxicity has not been explored. *Cosmos caudatus* extract attenuates doxorubicin-induced renal histopathological injury in female Wistar rats; therefore, this study aimed to evaluate whether ethanolic *C. caudatus* extract attenuates doxorubicin-induced renal histopathological injury in female Wistar rats, providing preclinical evidence for its potential role as a supportive renoprotective strategy during anthracycline exposure. The potential impact of this research lies in providing preliminary scientific evidence for the development of a natural product–based renoprotective strategy that is safe, accessible, and potentially integrable into anthracycline-based chemotherapy regimens. The findings are expected to pave the way for further studies, including testing in tumor-bearing models and future clinical trials, with the ultimate goals of reducing renal

complications, improving treatment continuity, and enhancing the quality of life for cancer patients.

METHOD

Preparation of Ethanolic *Cosmos caudatus* Extract

Aerial parts of *C. caudatus* were collected from Malang, Indonesia and taxonomically authenticated at Herbal Materia Medica Laboratory, Batu, Indonesia. A voucher specimen was deposited in the same herbarium (Voucher ID: 000.9.3/72/102.20/2025) to ensure traceability and reproducibility. The plant material was rinsed to remove debris, shade-dried under light-protected conditions until a constant weight was reached, and then milled to a uniform powder to improve extraction efficiency and batch homogeneity.

The powdered material was extracted using ethanol 96% *v/v* by maceration with intermittent agitation (plant-to-solvent ratio: 1:10 *w/v*) for 72 hours at room temperature. The extraction was repeated to maximize recovery of ethanol-soluble constituents, and the pooled extracts were filtered through Whatman No. 1 to remove particulate matter. The combined filtrates were concentrated under reduced pressure using a rotary evaporator. The resulting concentrate was further dried to obtain a stable crude ethanolic extract. The final extract was stored in airtight, light-resistant containers at -20°C until use (Aska et al., 2025; Kristijanto et al., 2025; Sari et al., 2024; Soetedjo et al., 2024).

For *in vivo* administration, the extract was freshly reconstituted each day in a suitable oral vehicle (0.5% CMC-Na) to achieve the intended dose and to maintain uniform dispersion throughout dosing. Suspensions were prepared immediately prior to gavage, mixed thoroughly to ensure homogeneity, and administered at a standardized dosing volume.

Study Design, Ethics, Animals, and Treatment Protocol

This study employed a preventive *in vivo* design to assess whether ethanolic *C. caudatus* extract mitigates doxorubicin-induced renal histopathological injury. Female Wistar rats (6-8 weeks; 220-280 g) were used and acclimatized prior to experimentation. Animals were housed under standard controlled conditions with *ad libitum* access to standard chow and water, and were monitored daily for clinical condition and treatment tolerance.

All procedures were conducted in accordance with institutional and national regulations governing laboratory animal welfare and were approved by the Institutional Animal Care and Use Committee/Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya (Approval No. 120/SLE/FK/UWKS/2025). Body weight was recorded at scheduled intervals to guide dose calculations and to provide a global index of systemic toxicity.

Rats were allocated into three experimental groups (n = 5 per group): NC (normal control), receiving vehicle only; DOX (doxorubicin), receiving doxorubicin 5 mg/kg intraperitoneally (i.p.) once weekly for 4 weeks (cumulative dose 20 mg/kg); and DOX+CCE (doxorubicin + *C. caudatus* extract), receiving ethanolic *C. caudatus* extract 200 mg/kg by oral gavage once daily for 1 week prior to doxorubicin administration, followed by concurrent doxorubicin exposure using the same

schedule (5 mg/kg i.p., once weekly for 4 weeks) while continuing daily extract treatment throughout the doxorubicin period. This regimen was selected to model repeated anthracycline exposure and to specifically test an extract strategy initiated before injury induction and maintained during toxicant challenge.

Kidney Collection and Histopathology

At study completion, rats were anesthetized with a ketamine-xylazine combination and euthanized in accordance with the approved animal ethics protocol. Once surgical anesthesia was confirmed, a midline laparotomy was performed and the left kidney was rapidly excised to limit post-mortem autolysis. The tissue was gently rinsed with cold physiological saline to remove surface blood, trimmed of adherent fat and connective tissue, and immediately fixed in 10% neutral-buffered formalin for adequate preservation of renal microarchitecture. Fixed tissues were processed using routine histological workflows (graded dehydration, clearing, and paraffin embedding). Paraffin blocks were sectioned at 4-5 μm and mounted on glass slides.

Sections were stained with hematoxylin and eosin (H&E) and evaluated by a board-certified/experienced pathologist blinded to group allocation. Histological assessment was performed using a light microscope (Olympus BX51; Olympus, Tokyo, Japan) at 100× and 400× magnifications (objective 10× and 40×; total magnification 100× and 400×) to systematically examine glomerular and tubulointerstitial compartments. Renal injury severity was graded semi-quantitatively using the EGTI scoring system, which captures lesions across endothelial, glomerular, tubular, and interstitial domains (Table 1) (Brown, 2024). Representative cortical regions were assessed across multiple non-overlapping fields per section (10 fields/animal), and each EGTI domain was scored according to predefined criteria. Domain scores were subsequently compiled to generate an overall EGTI-based injury profile for each animal for statistical comparisons.

Table 1. The EGTI scoring system.

Tissue	Lesions Criteria	Score
Endothelium	No damage	0
	Endothelial swelling	1
	Endothelial disruption	2
	Loss of endothelium	3
Glomerulus	No damage	0
	Thickening of Bowman's Capsule	1
	Glomerular retraction	2
	Glomerular fibrosis	3
Tubules	No damage	0
	Loss of Brush Border < 25% of tubular cells at basement membrane	1
	Loss of Brush Border > 25% of tubular cells, basement membrane thickening	2
	Inflammation, necrosis ≤ 60% of tubular cells	3
	Necrosis > 60% of tubular cells	4
Interstitial	No damage	0

Tissue	Lesions Criteria	Score
	Inflamation or hemorrhage < 25% of tissue	1
	Necrosis < 25% of tissue	2
	Necrosis 25-60% of tissue	3
	Necrosis > 60% of tissue	4

Statistical Analysis

All analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation (SD). Differences among groups were evaluated using a two-way analysis of variance (two-way ANOVA), with treatment group and lesion domain (endothelium, glomerulus, tubules, interstitium) included as fixed factors, followed by Tukey's post hoc multiple-comparisons procedure to identify pairwise differences when significant main effects and/or interactions were detected. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

This study evaluated whether ethanolic *C. caudatus* extract confers structural protection against doxorubicin-associated renal injury in female Wistar rats. Representative H&E-stained kidney sections illustrate clear group-wise differences in cortical architecture. In the NC group (Figure 1A), renal morphology is largely preserved, with intact tubular profiles, minimal interstitial cellularity, and no overt structural disruption. In contrast, kidneys from the DOX group (Figure 1B) demonstrate a pattern consistent with toxic renal injury, characterized by widespread tubular epithelial alteration (including epithelial swelling/degeneration with luminal irregularity), accompanied by prominent tubulointerstitial involvement, as reflected by increased interstitial cellular infiltrates and associated architectural disorganization. In the DOX+CCE group (Figure 1C), overall renal architecture appears comparatively better maintained, with less conspicuous tubulointerstitial cellularity and reduced severity of tubular epithelial injury relative to doxorubicin alone, supporting a qualitative renoprotective effect of *C. caudatus* co-treatment.

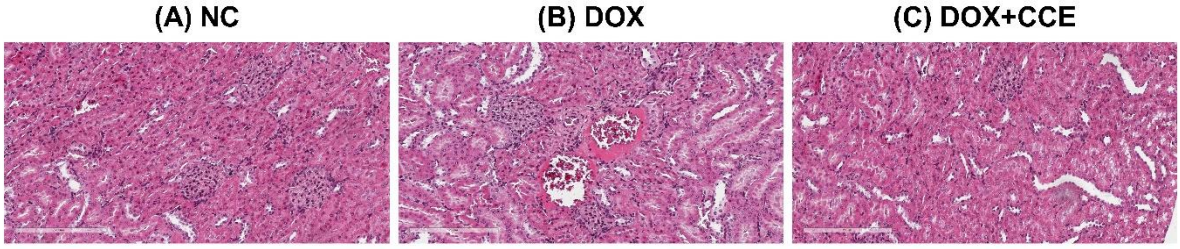

Figure 1. Representative renal histopathology following doxorubicin exposure and ethanolic *Cosmos caudatus* co-treatment in female Wistar rats. Representative hematoxylin and eosin (H&E)-stained kidney sections from (A) normal control rats (NC), (B) doxorubicin-treated rats (DOX; 5 mg/kg i.p., once weekly for 4 weeks; cumulative 20 mg/kg), and (C) rats receiving *C. caudatus* extract with doxorubicin (DOX+CCE; 200 mg/kg/day by oral gavage; 1-week pretreatment followed by concurrent daily dosing during the 4-week doxorubicin regimen). Images

illustrate preserved cortical architecture in NC, diffuse tubular and tubulointerstitial injury features in DOX, and relative attenuation of these changes with *C. caudatus* co-treatment. Scale bar: 200 µm.

Furthermore, semi-quantitative scoring using the EGTI framework demonstrated that doxorubicin exposure produced a clear and consistent aggravation of renal structural injury across all compartments evaluated (endothelial, glomerular, tubular, and interstitial). As shown in Figure 2, the DOX group exhibited significantly higher lesion scores than the normal control (NC) for each EGTI domain (all $p < 0.0001$), indicating broad microvascular, glomerular, and tubulointerstitial involvement rather than a compartment-restricted pattern of damage.

Importantly, co-administration of ethanolic *C. caudatus* extract (DOX+CCE) significantly attenuated the severity of injury in every domain compared with doxorubicin alone, with the strongest effect observed in tubulointerstitial parameters (endothelium $p = 0.0071$; glomerulus $p = 0.0240$; tubules $p = 0.0018$; interstitial $p = 0.0004$). These domain-level improvements translated into a marked reduction in the total EGTI score in the DOX+CCE group versus DOX ($p < 0.0001$), reflecting an overall mitigation of doxorubicin-associated renal histopathological burden. Despite this protection, scores in the DOX+CCE group remained higher than NC, suggesting partial, rather than complete, normalization of renal architecture under the present regimen.

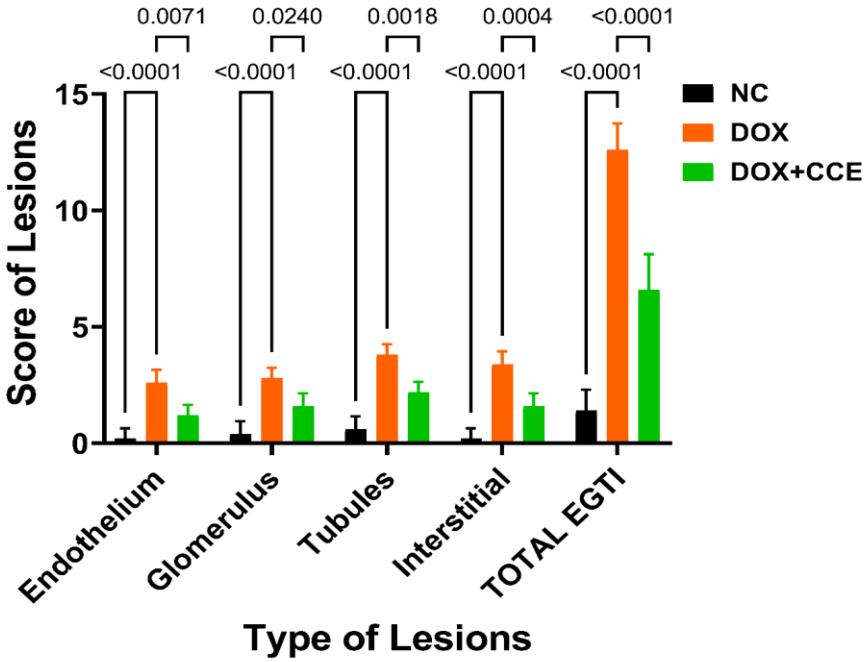

Figure 2. Ethanolic *Cosmos caudatus* extract attenuates doxorubicin-induced renal histopathological injury in female Wistar rats (EGTI scoring). EGTI scores for endothelium, glomerulus, tubules, and interstitium, together with the total EGTI score, are shown for normal control rats (NC), doxorubicin-treated rats (DOX; 5 mg/kg i.p., once weekly for 4 weeks, cumulative 20 mg/kg), and rats receiving *C. caudatus* extract with doxorubicin (DOX+CCE; 200 mg/kg/day by oral gavage, 1-week pretreatment followed by concurrent daily dosing during the 4-week doxorubicin regimen). Bars represent mean ± SD (n = 5/group). Statistical analysis was

performed using two-way ANOVA followed by Tukey's multiple-comparisons test. Exact *p*-values are indicated above brackets.

The present work sits within a clinically relevant problem that is often underemphasized in anthracycline safety narratives: kidney injury can become a practical constraint on cancer therapy, not only through acute complications but also by narrowing subsequent treatment options and complicating supportive care. Contemporary hospital-based data underscore that AKI is a recurring event in oncology practice, with sizeable cohorts reporting non-trivial incidence among cancer admissions (Kang et al., 2021; Lu et al., 2025; Nazzal et al., 2022). Against this backdrop, experimental models remain important for clarifying which renal compartments are most vulnerable to doxorubicin exposure and for testing candidate protective strategies that could be integrated without compromising the core antitumor regimen.

A key strength of this study is the use of the EGTI framework to interrogate renal injury across microvascular, glomerular, tubular, and interstitial domains, rather than relying on a single compartment readout. The EGTI approach was developed and subsequently adopted in multiple animal kidney-injury settings because it captures injury heterogeneity while remaining operationally feasible for blinded histological scoring; importantly, prior work links EGTI patterns to functional impairment and canonical renal injury markers in experimental models (Havakhah et al., 2018). In practical terms, this matters because doxorubicin nephrotoxicity is not a purely "tubular" phenomenon, its involves endothelial dysfunction, podocyte/glomerular stress, and tubulointerstitial inflammation operating in concert, and a compartmental scoring system is well-suited to reflect that complexity (Abd-Ellatif et al., 2022; Arozal et al., 2025).

Mechanistically, the renal phenotype observed in doxorubicin exposure is consistent with a literature that places oxidative stress and inflammatory amplification at the center of anthracycline tissue injury (Abd-Ellatif et al., 2022; Afsar et al., 2020; Lu et al., 2025). Doxorubicin undergoes redox cycling and can drive excessive reactive oxygen species generation, which propagates lipid peroxidation, mitochondrial dysfunction, and downstream cell-death signaling; these changes are coupled to inflammatory pathway activation (including NF-κB and inflammasome-related mediators) that sustains tissue injury beyond the initial insult (Kciuk et al., 2023; Meng et al., 2019). In the kidney, endothelial disruption has disproportionate consequences because microvascular injury impairs perfusion and oxygen delivery, which in turn sensitizes proximal tubules, cells with high metabolic demand, to degeneration and necrosis. This "vascular-tubular" coupling offers a coherent explanation for why doxorubicin-associated damage can present as a multi-compartment process rather than an isolated lesion type (Gad et al., 2025).

Within that pathobiological context, the protective signal seen with *C. caudatus* is biologically promising. *Cosmos caudatus* is an edible medicinal plant with a phytochemical profile enriched in polyphenols and flavonoids, compounds repeatedly associated with antioxidant and anti-inflammatory bioactivity (Ahda et al., 2023; Latiff et al., 2021; Sari et al., 2024). Human and experimental nutrition literature describes *C. caudatus* as containing constituents such as quercetin and chlorogenic acid derivatives, catechins, and proanthocyanidins, alongside antioxidant capacity measurable across standard assays (Sari et al., 2024; You et al., 2021). More recent metabolomics

work further supports that extraction method and solvent influence the breadth and abundance of these metabolites, and ethanol-based preparations commonly recover a spectrum of phenolic and flavonoid compounds consistent with redox-modulating potential (Rafi et al., 2023; Wan-Nadilah et al., 2019). Although the present study was not designed to pinpoint a single causal molecule, the collective phytochemical evidence supports the interpretation that the extract could buffer doxorubicin-triggered redox stress and temper inflammatory signaling, two upstream drivers repeatedly implicated in anthracycline nephropathy.

The preventive dosing strategy, brief pretreatment followed by continued exposure during the doxorubicin course, also aligns with how redox-sensitive cytoprotective programs operate. A frequently discussed axis is the Nrf2 pathway, which coordinates transcriptional programs for antioxidant defense and detoxification enzymes and is widely considered a gatekeeper against oxidative tissue injury (Huang et al., 2023; Rizq et al., 2023). In several models of renal stress, interventions that strengthen antioxidant capacity before the insult (or sustain it during exposure) are more likely to blunt the downstream cascade of mitochondrial dysfunction, inflammation, and structural breakdown than approaches initiated only after injury is established (Kang et al., 2021). From a translational perspective, this is clinically intuitive: prophylactic supportive strategies are most valuable when they maintain organ reserve early, rather than attempting to reverse established histological injury late in the treatment cycle.

An additional point of interest is the exclusive use of female rats. Sex-related variability in doxorubicin toxicity has been documented in preclinical systems, with several reports suggesting relative protection in females in certain contexts, potentially reflecting differences in baseline redox homeostasis, hormonal modulation of inflammatory signaling, or drug handling (Agostinucci et al., 2023; Grant et al., 2019). While this literature does not imply uniform protection across all injury models, it does argue that evaluating renoprotective candidates in females is not a minor design choice, particularly when anthracyclines remain central to treatment in malignancies with substantial female burden. Future studies that directly compare sexes, or incorporate hormone status, would be valuable for clarifying how generalizable the protective profile of *C. caudatus* is across biological contexts.

Several limitations should be acknowledged to appropriately frame interpretation and next steps. First, histopathological scoring provides an integrated structural endpoint, but mechanistic inference remains indirect without accompanying renal function indices (e.g., creatinine/urea), tubular injury biomarkers (e.g., KIM-1/NGAL), or oxidative–inflammatory panels that map the injury cascade more explicitly. The EGTI system itself has been used in settings where such biomarkers are available and correlate with tissue scores, which makes those additions particularly informative for strengthening causal interpretation. Second, the study used a single extract dose; dose-response mapping and extract standardization (e.g., marker-based quantification or chromatographic fingerprinting) would increase reproducibility and help delineate the therapeutic window, especially important for botanicals where composition varies with geography, harvest conditions, and extraction parameters. Third, because the scoring outcomes are semi-quantitative, future confirmatory work may benefit from complementary quantitative histomorphometry and

from statistical strategies that explicitly accommodate ordinal endpoints, particularly when sample sizes are modest.

Finally, the broader translational question is not only whether a botanical extract can reduce organ injury, but whether it can do so without diminishing anticancer efficacy or introducing clinically meaningful drug-herb interactions. This is a recurrent issue in the supportive-care literature: antioxidants can be protective in normal tissues, yet their interaction with chemotherapy-induced oxidative stress in tumor cells is context-dependent. Accordingly, the most persuasive next step would be to *test C. caudatus* alongside doxorubicin in a tumor-bearing model (or paired *in vitro* systems) to verify that organ protection does not come at the expense of antitumor activity, while also characterizing pharmacokinetic interactions where relevant.

CONCLUSION

This study supports the concept that C. caudatus, an edible plant with a well-described polyphenol/flavonoid signature, has credible biological rationale as a renoprotective adjunct during anthracycline exposure. The compartment-resolved histological approach strengthens the interpretation that protection is not confined to a single renal niche, and it provides a framework for future work that integrates functional biomarkers, molecular pathway mapping, and oncologic efficacy testing to move from histological protection toward translational readiness.

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