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Ethanolic *Cosmos caudatus* Extract Mitigates Doxorubicin-Induced Serum Lipid Profile Derangements in Female Wistar Rats

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Abstract
This study investigated whether an ethanolic extract of *Cosmos caudatus* can mitigate *doxorubicin*-associated serum lipid derangements in female Wistar rats. Fifteen female Wistar rats (6–8 weeks; 220–280 g) were allocated to three groups (n=5/group): control (vehicle), *doxorubicin* (5 mg/kg i.p., once weekly for 4 weeks), or *C. caudatus* plus *doxorubicin* (200 mg/kg/day oral gavage for 1 week pre-treatment, followed by continued daily extract with concurrent *doxorubicin* for 4 weeks). At the study's end, serum total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) were measured using enzymatic colorimetric assays; groups were compared using one-way ANOVA with Tukey's post hoc test (two-tailed, $\alpha = 0.05$). *Doxorubicin* induced a pronounced dyslipidemic profile versus controls, increasing TC (118 ± 10 vs. 78 ± 7.2 mg/dL; $p < 0.0001$) and TG (128 ± 20 vs. 71 ± 10 mg/dL; $p < 0.0001$), reducing HDL-C (36 ± 4.3 vs. 52 ± 4.6 mg/dL; $p < 0.0001$), and elevating LDL-C (41 ± 8.4 vs. 17 ± 3.7 mg/dL; $p < 0.0001$). *Cosmos caudatus* treatment significantly attenuated these abnormalities compared with *doxorubicin* alone (TC 98 ± 9.8 mg/dL, $p = 0.0138$; TG 100 ± 11 mg/dL, $p = 0.0268$; HDL-C 45 ± 2.7 mg/dL, $p = 0.0148$; LDL-C 29 ± 4.8 mg/dL, $p = 0.0191$), supporting partial normalization toward a less atherogenic lipid profile. These findings suggest that ethanolic *C. caudatus* may be a promising botanical adjunct to reduce anthracycline-associated dyslipidemia.
Keywords: doxorubicin; dyslipidemia; *Cosmos caudatus*; anthracycline

INTRODUCTION

Here's the proofread passage. I corrected minor grammatical issues (e.g., parallel structure, article usage, punctuation for clarity and consistency), improved sentence flow for conciseness and academic precision, ensured tense consistency in past tense where reporting prior work, and retained all citations, paragraph structure, and context. Non-English terms like species names (*Cosmos caudatus*), local names (*ulam raja*, *kenikir*), and the title phrase (*Ethanolic Cosmos caudatus Extract Mitigates Doxorubicin-Induced Serum Lipid Profile Derangements in Female Wistar Rats*) are italicized as requested.

Cancer remains a dominant global health challenge, with an estimated 19,976,499 new cases and 9,743,832 deaths worldwide in 2022 (Bray et al., 2024). Among women, breast cancer accounts for 2,296,840 new cases (approx. 23.8% of female cancers), underscoring the sustained need for effective systemic therapy alongside long-term toxicity mitigation strategies (Gu et al., 2025). In this context, anthracyclines, particularly doxorubicin, continue to be widely deployed across solid and hematologic malignancies—including metastatic breast cancer and lymphomas—because of their proven antitumor efficacy (Douedi & Carson, 2025).

However, as survival improves, attention has shifted from short-term tumor control alone to the broader consequences of therapy on cardiovascular and metabolic health. Contemporary cardio-oncology highlights that anthracycline exposure can precipitate acute and chronic

cardiovascular injury and also interacts with modifiable cardiometabolic risk factors that shape long-term outcomes (Belger et al., 2024; Kciuk et al., 2023). While anthracycline cardiotoxicity is often discussed through imaging and myocardial injury pathways, anthracycline-treated populations also show a substantial burden of conventional risk factors such as dyslipidemia, which may be under-recognized and undertreated (Abrahams et al., 2025; da Cunha Menezes Souza et al., 2021; Klinnikova et al., 2016). This matters because cardiovascular risk factors tend to amplify therapy-related toxicity over time, increasing the likelihood of late cardiovascular morbidity among cancer survivors.

Emerging survivorship data illustrate how common lipid abnormalities can be after anthracycline therapy. In a recent cohort of childhood, adolescent, and young adult cancer survivors treated with anthracyclines, dyslipidemia was present in 52.9% overall and 51.7% among those younger than 20 years, with marked underdiagnosis compared with measured lipid panels (Dean et al., 2025). These observations strengthen the rationale for proactive strategies that prevent or reverse lipid derangements during and after cardiotoxic cancer therapy, particularly in settings where survivors may carry cardiovascular risk for decades.

Mechanistically, doxorubicin toxicity is not restricted to a single organ system. Beyond direct cardiomyocyte injury, anthracyclines generate oxidative stress and disrupt mitochondrial and inflammatory signaling—processes that can extend to metabolic organs and systemic biochemistry (Linders et al., 2024). In experimental models, doxorubicin has been repeatedly associated with atherogenic lipid shifts, typically characterized by elevations in total cholesterol and triglycerides with adverse changes in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) fractions—patterns consistent with a pro-atherogenic milieu (Ifeanacho et al., 2021). These disturbances are biologically reasonable given that oxidative stress and inflammatory signaling influence hepatic lipid handling, lipoprotein remodeling, and peripheral lipid utilization (Pieniążek et al., 2013). From a translational standpoint, chemotherapy-associated dyslipidemia is not merely a laboratory curiosity; it may contribute to the long-term vascular risk profile of survivors, especially when layered on top of anthracycline-related myocardial vulnerability.

Natural products rich in polyphenols have attracted attention as adjunctive candidates to counter oxidative and metabolic perturbations induced by cytotoxic therapies. *Cosmos caudatus* (commonly known as *ulam raja* or *kenikir*) is an edible herb widely consumed in parts of Southeast Asia and also used in traditional medicine (Cheng et al., 2015; Latiff et al., 2021). Phytochemical studies indicate that *C. caudatus* is a meaningful dietary source of phenolic compounds and flavonoids with antioxidant potential. Importantly for lipid-focused outcomes, *ethanolic extracts of C. caudatus* have demonstrated metabolic activity *in vivo*. In a high-fat diet rat model, an *ethanolic extract* improved obesity-related biomarkers and significantly improved plasma lipid profiles, and nuclear magnetic resonance (NMR) profiling identified constituents such as catechin, quercetin, rutin, kaempferol, and chlorogenic acid—compounds frequently linked to antioxidant and lipid-modulating effects (Hafifi, 2015; Rahman et al., 2017; Wan-Nadilah et al., 2019; Zahara et al., 2024). Additional analytical work has reinforced the presence of key flavonoids (notably rutin and quercetin) in *ethanolic C. caudatus extracts*, supporting the possibility of systemic bioactivity relevant to lipid metabolism (Rafi et al., 2023).

Despite this growing body of phytochemical and preclinical evidence, targeted evaluation of *C. caudatus* as a countermeasure for doxorubicin-associated dyslipidemia remains limited. This gap is relevant because lipid derangements represent a measurable, clinically meaningful phenotype that bridges metabolic toxicity with cardiovascular risk—an intersection increasingly emphasized in survivorship care.

The novelty of this study lies in three key contributions. First, this is the first experimental investigation specifically designed to evaluate the lipid-protective effects of *ethanolic Cosmos caudatus extract* in a doxorubicin-induced dyslipidemia model, addressing a previously unexplored intersection between a polyphenol-rich botanical and anthracycline metabolic toxicity. Second, unlike prior studies that examined *C. caudatus* primarily in obesity or metabolic syndrome models, the current work focuses on chemotherapy-induced dyslipidemia—a distinct pathophysiological context characterized by oxidative stress, mitochondrial dysfunction, and inflammatory signaling rather than diet-induced metabolic overload. Third, by employing a comprehensive lipid panel (TC, TG, HDL-C, LDL-C) and establishing both pre-treatment and concurrent dosing protocols, this study provides mechanistic insight into the temporal dynamics of botanical intervention against anthracycline-associated lipid derangements, which has direct translational implications for adjunctive cardioprotective strategies in cancer survivorship.

Therefore, the present study investigates whether *ethanolic C. caudatus extract* can mitigate doxorubicin-induced serum lipid profile derangements in female Wistar rats, focusing on standard lipid parameters (total cholesterol [TC], triglyceride [TG], LDL-C, and HDL-C). Given the global cancer burden and the enduring role of anthracyclines in common female malignancies, clarifying the lipid-modulating potential of a polyphenol-rich, food-derived botanical may inform future strategies aimed at reducing therapy-related cardiometabolic risk.

RESEARCH METHODS

Preparation and extraction of *Cosmos caudatus* aerial parts

Fresh aerial parts of *C. caudatus* (leaves and tender stems) were obtained from Surabaya, Indonesia in July, 2025. The plant material was authenticated by Laboratorium Herbal Materia Medica, Dinas Kesehatan Provinsi Jawa Timur, Batu, Jawa Timur, Indonesia and a voucher specimen (No. 000.9.3/72/102.20/2025) was deposited for future reference. The samples were rinsed with running water to remove debris, blotted dry, and air-dried under shade with adequate ventilation, followed by drying in a circulating oven at 40 °C until a constant weight was achieved. The dried material was milled into a fine powder and stored in airtight, light-protected containers at room temperature until extraction.

Powdered plant material was extracted using 96% ethanol at a 1:10 (w/v) ratio. Extraction was performed by maceration with continuous agitation at room temperature for 72 h, and the residue was re-extracted twice under identical conditions to maximize recovery of ethanol-soluble constituents. Combined filtrates were passed through filter paper, then concentrated under reduced pressure using a rotary evaporator at ≤40 °C to remove ethanol. The resulting crude extract was further dried to constant mass (low-temperature drying). The dried ethanolic extract was aliquoted to minimize repeated freeze-thaw cycles and stored at −20 °C in amber containers until use. For animal administration, the extract was freshly reconstituted in 0.5%

carboxymethylcellulose to the required concentration immediately before dosing (Aska et al., 2025; Kristijanto et al., 2025; Soetedjo et al., 2024).

Ethical consideration, animals, and intervention

All animal procedures were conducted in accordance with internationally accepted standards for laboratory animal care and use. Ethical approval was obtained Ethical Unit, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia (Approval No: 120/SLE/FK/UWKS/2025). Female Wistar rats (n = 15) with a starting body weight of 220-280 g (6-8 weeks old) were housed under standard controlled conditions with ad libitum access to chow and water, following an acclimatization period of 7 days. Animals were observed daily for general health, behavior, and signs of treatment-related distress, and body weight was recorded at regular intervals throughout the experiment.

Rats were allocated into three experimental groups (n = 5 per group): CTRL (control), which received vehicle only; DOXO (doxorubicin), which received doxorubicin at 5 mg/kg body weight, intraperitoneally (i.p.), once weekly for 4 weeks (cumulative dose 20 mg/kg); and DOXO+CC200 (extract + doxorubicin), which received ethanolic *C. caudatus* extract 200 mg/kg body weight by oral gavage once daily for 1 week, followed by concurrent administration of doxorubicin (5 mg/kg i.p., once weekly for 4 weeks) while continuing daily *C. caudatus* treatment throughout the doxorubicin exposure period. The doxorubicin dosing schedule was selected to reflect a commonly used repeated-dose anthracycline regimen in rats. Humane endpoints were predefined, and any animal showing severe or persistent distress would be removed from the study and euthanized according to the approved protocol.

Measurement of serum lipid profile

At the end of the experimental period, rats were fasted for 8 h with free access to water and then euthanized under deep anesthesia using a ketamine-xylazine combination (i.p.), in accordance with institutional animal-welfare approval and established euthanasia guidance. Once a surgical plane of anesthesia was confirmed (absence of pedal withdrawal and corneal reflexes), whole blood was collected by cardiac puncture into plain tubes. Serum was separated after clotting at room temperature for 30 min and centrifugation at 3,000 × g for 15 min, then aliquoted and stored at -80 °C until analysis to minimize degradation from repeated freeze-thaw cycles.

Serum TC and TG were quantified using enzymatic colorimetric kits from Elabscience® (Elabscience Bionovation Inc., Houston, TX, USA). TC was measured using the Total Cholesterol (TC) Colorimetric Assay Kit (Single Reagent, COD-PAP Method; Cat. No. E-BC-K109-S), and TG using the Triglyceride (TG) Colorimetric Assay Kit (Single Reagent, GPO-PAP Method; Cat. No. E-BC-K261-S), with absorbance read at 510 nm according to the manufacturer's instructions. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined using double-reagent colorimetric kits (HDL-C: Cat. No. E-BC-K221-M; LDL-C: Cat. No. E-BC-K205-M) with absorbance measured at 546 nm. Concentrations were calculated using the kit-provided formulas. Results were reported in mg/dL; where outputs were generated in mmol/L, values were converted to mg/dL using standard conversion factors.

Statistical analysis

All analyses were performed using GraphPad Prism (GraphPad Software, San Diego, CA, USA). Continuous data (TC, TG, HDL-C, and LDL-C) were summarized as mean ±

standard deviation (SD). Normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Levene's test. When assumptions for parametric testing were satisfied, group differences were examined by one-way analysis of variance (ANOVA) followed by Tukey's multiple-comparisons post hoc test. If assumptions were not met, data were analyzed using the Kruskal-Wallis test with Dunn's post hoc correction for multiple comparisons. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

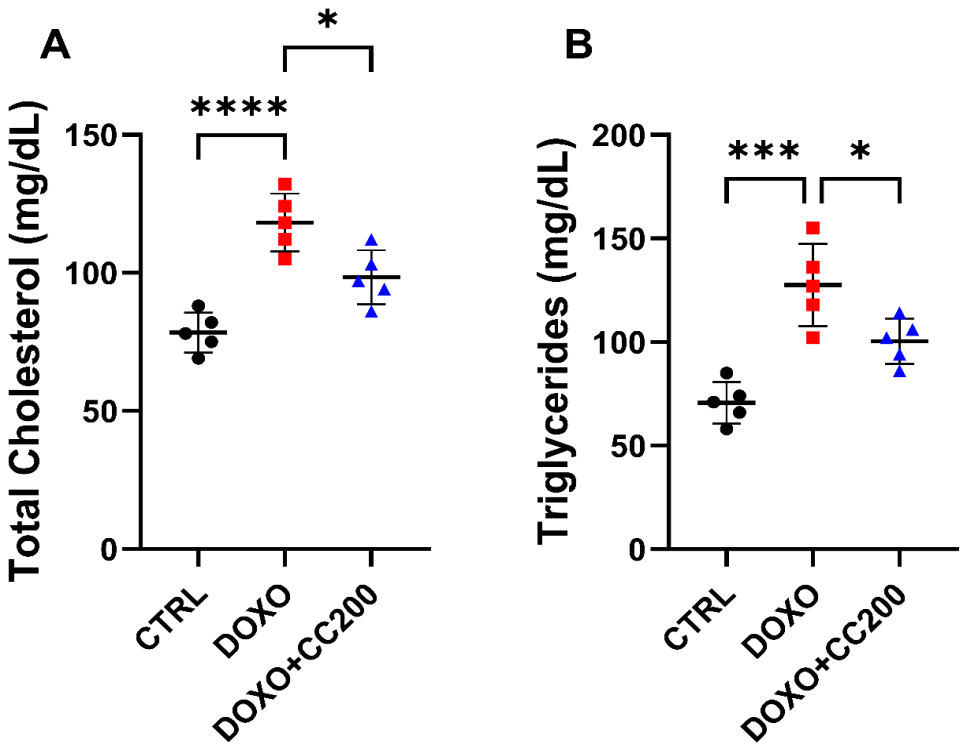

Figure 1. Ethanolic *Cosmos caudatus* extract mitigates doxorubicin-induced elevations in serum lipids in female Wistar rats. (A) Serum total cholesterol (TC) and (B) serum triglycerides (TG) in control rats (CTRL), doxorubicin-treated rats (DOXO; 5 mg/kg i.p., once weekly for 4 weeks), and rats receiving *C. caudatus* extract (200 mg/kg/day by oral gavage) with doxorubicin (DOXO+CC200; 1-week pre-treatment followed by concurrent dosing during the 4-week doxorubicin regimen). Each symbol represents one animal (n = 5/group); horizontal lines indicate mean and error bars denote standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple-comparisons test. Significance is shown as indicated: **** $p < 0.0001$; *** $p < 0.001$; * $p < 0.05$.

Doxorubicin exposure significantly altered TC and TG levels in female Wistar rats (Figure 1). For TC (Figure 1A), the DOXO group showed a marked increase compared with CTRL (CTRL: 78 ± 7.2 mg/dL vs DOXO: 118 ± 10 mg/dL; $p < 0.0001$), indicating that repeated doxorubicin administration induced a hypercholesterolemic shift. Co-treatment with ethanolic *C. caudatus* extract (200 mg/kg; DOXO+CC200) significantly reduced TC relative to DOXO alone (DOXO+CC200: 98 ± 9.8 mg/dL; DOXO vs DOXO+CC200: $p = 0.0138$),

with values trending toward the control range. Moreover, a comparable pattern was observed for TG (Figure 1B). Triglyceride concentrations were significantly higher in the DOXO group than in CTRL (CTRL: 71 ± 10 mg/dL vs DOXO: 128 ± 20 mg/dL; $p < 0.0001$). Administration of *C. caudatus* (200 mg/kg) attenuated this increase, with DOXO+CC200 showing lower TG than the DOXO-only group (DOXO+CC200: 100 ± 11 mg/dL; DOXO vs DOXO+CC200: $p = 0.0268$).

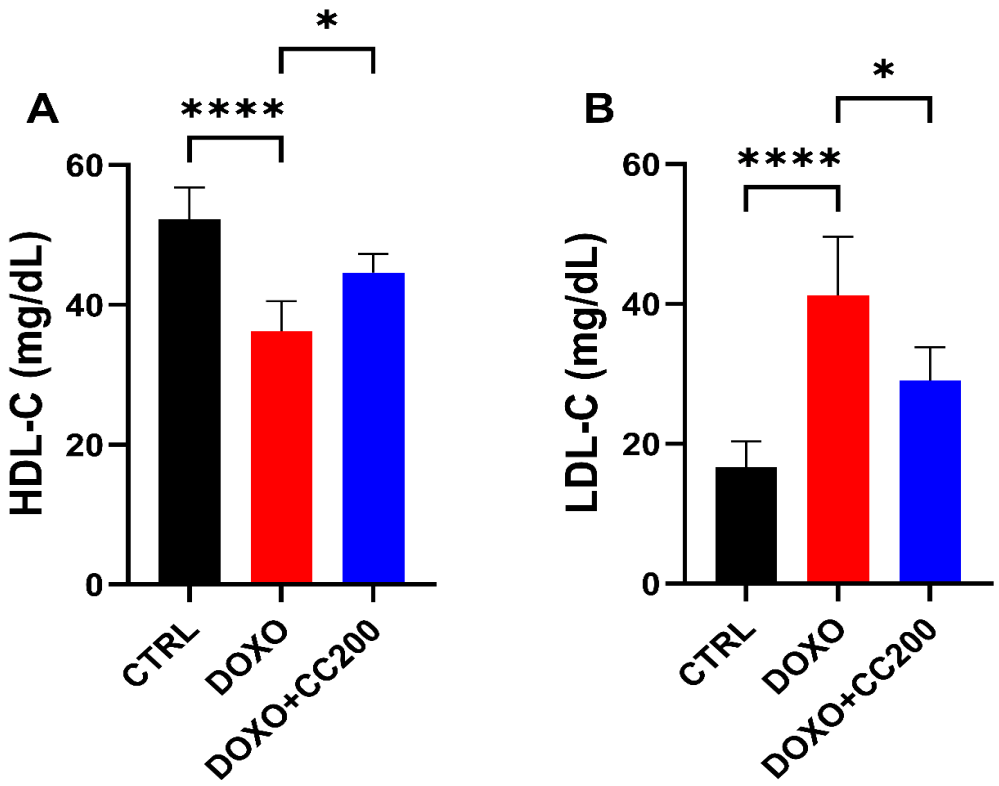

Figure 2. Ethanolic *Cosmos caudatus* extract attenuates doxorubicin-induced lipoprotein disturbances in female Wistar rats. (A) Serum high-density lipoprotein cholesterol (HDL-C) and (B) serum low-density lipoprotein cholesterol (LDL-C) in control rats (CTRL), doxorubicin-treated rats (DOXO; 5 mg/kg i.p., once weekly for 4 weeks), and rats receiving *C. caudatus* extract (200 mg/kg/day by oral gavage) with doxorubicin (DOXO+CC200; 1-week pre-treatment followed by concurrent dosing during the 4-week DOXO regimen). Bars represent mean and error bars denote standard deviation (SD) (n = 5/group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple-comparisons test. Significance is shown as indicated: **** $p < 0.0001$; * $p < 0.05$.

Furthermore, doxorubicin significantly disrupted lipoprotein fractions in female Wistar rats (Figure 2). For HDL-C (Figure 2A), doxorubicin caused a clear reduction relative to controls (CTRL: 52 ± 4.6 mg/dL vs DOXO: 36 ± 4.3 mg/dL; $p < 0.0001$), consistent with a shift toward a less favorable lipoprotein profile. Treatment with ethanolic *C. caudatus* extract (200 mg/kg; DOXO+CC200) significantly increased HDL-C compared with the DOXO-only group (DOXO+CC200: 45 ± 2.7 mg/dL; DOXO vs DOXO+CC200: $p = 0.0148$), indicating partial restoration toward the control range. With regards to LDL-C (Figure 2B), the DOXO group exhibited a marked increase compared with controls (CTRL: 17 ± 3.7 mg/dL vs DOXO: 41 ± 8.4 mg/dL; $p < 0.0001$). Co-treatment with *C. caudatus* significantly reduced LDL-C

relative to doxorubicin alone (DOXO+CC200: 29 ± 4.8 mg/dL; DOXO vs DOXO+CC200: $p = 0.0191$), again supporting mitigation of the atherogenic shift induced by doxorubicin. Together, these findings show that doxorubicin induces a lipoprotein pattern characterized by lower HDL-C and higher LDL-C, while ethanolic *C. caudatus* at 200 mg/kg partially normalizes both fractions.

Anthracyclines remain foundational in the treatment of many solid and hematologic malignancies, yet their use is constrained by dose-limiting toxicities that extend beyond the myocardium and may influence long-term cardiometabolic health (Douedi & Carson, 2025). In survivorship cohorts, cardiovascular risk factors, including dyslipidemia, are increasingly recognized as common and often undertreated after anthracycline exposure, supporting the clinical relevance of adjunct strategies that preserve metabolic homeostasis without compromising antitumor therapy (Dean et al., 2025). Against this backdrop, the present work adds experimental evidence that a plant-derived intervention can blunt the atherogenic lipid shifts that accompany doxorubicin exposure, a phenotype repeatedly described in rodent models and proposed to contribute to downstream cardiovascular vulnerability.

Mechanistically, anthracycline-associated dyslipidemia is plausibly multifactorial (Belger et al., 2024; de Jesus et al., 2022). Doxorubicin is well known to provoke oxidative and nitrosative stress, mitochondrial dysfunction, and inflammatory signaling, which can disrupt systemic energy handling and lipid trafficking (Schirone et al., 2022). While cardiotoxicity is the dominant clinical concern, emerging evidence indicates that anthracycline exposure can also alter hepatic and whole-body metabolism, including pathways governing triglyceride synthesis, lipoprotein assembly, and fatty-acid oxidation, processes that would be expected to shift circulating TC, TG, and LDL/HDL balance (de Jesus et al., 2022). In that context, attenuation of lipid derangements may represent more than a biochemical improvement; it may reduce an additional, modifiable contributor to long-term cardiovascular risk during and after chemotherapy, complementing established surveillance efforts focused on ventricular function.

The biological plausibility of *C. caudatus* as a lipid-modulating adjuvant is supported by its phytochemical profile and prior metabolic studies. Ethanolic extracts of *C. caudatus* leaves have been characterized by metabolomics to contain polyphenols and flavonoids, including catechin, quercetin, rutin, kaempferol, and chlorogenic acid, compounds repeatedly linked to antioxidant capacity and cardiometabolic benefits (Ahda et al., 2023; Moshawih et al., 2017; Rafi et al., 2023). In an established high-fat diet model, ethanolic *C. caudatus* leaf extract demonstrated anti-obesity activity and was proposed to act partly through reduced intestinal lipid absorption and modulation of adipocyte-related pathways, offering a coherent rationale for improvements in serum lipid handling under metabolic stress (Rahman et al., 2017).

Beyond the plant as a whole, several constituents commonly reported in *C. caudatus* provide mechanistic anchors that align with the direction of lipid changes observed in doxorubicin models. Chlorogenic acid has been shown to lower cholesterol and attenuate fatty liver in hypercholesterolemic rats, with evidence implicating upregulation of lipid oxidation programs (e.g., PPAR-α-related signaling) (Ziółkiewicz et al., 2024). Rutin has demonstrated hypocholesterolemic effects in rodent hyperlipidemia models, including reductions in TC and LDL-C (Ganeshpurkar & Saluja, 2017). Quercetin intake has been reported to lower circulating lipids in experimental settings, potentially through enhanced hepatic lipid ω-oxidation and related transcriptional control (Hoek-van den Hil et al., 2013). Although the current study did

not quantify specific metabolites within the administered extract, these convergent lines of evidence support a model in which a polyphenol-rich ethanolic *C. caudatus* preparation counteracts anthracycline-driven oxidative and metabolic stress, thereby stabilizing lipoprotein metabolism rather than merely masking biochemical readouts.

The choice of female Wistar rats is also worth considering in interpretation and translation. Sex influences lipid metabolism and responses to metabolic stress in rodents, and there is substantial evidence for sex-related differences in susceptibility to doxorubicin toxicity, partly attributed to hormonal milieu and mitochondrial responses (Belger et al., 2024). This matters for two reasons: first, baseline lipid profiles and variance can differ by sex; second, an intervention that appears effective in females may behave differently in males, particularly if mechanisms intersect with oxidative stress signaling, mitochondrial turnover, or endocrine regulation (Patel et al., 2024). Future experiments designed a priori to test sex as a biological variable would strengthen generalizability.

Several limitations should be acknowledged to frame the scope of inference. The sample size reflects common practice for exploratory in vivo work but limits precision for effect estimation and increases sensitivity to inter-individual variability. More importantly, the study focuses on serum lipid endpoints without parallel assessment of hepatic lipid accumulation, apolipoproteins, inflammatory mediators, oxidative stress markers, or transcriptional regulators of lipid handling. Given that doxorubicin can perturb both cardiac and hepatic metabolic programs, integrating liver histology (e.g., steatosis scoring), oxidative stress indices, and targeted gene/protein analyses (e.g., PPAR-α/SREBP pathways) would help distinguish whether the extract primarily affects lipid absorption, synthesis, export, or oxidation. In addition, phytochemical standardization (e.g., total phenolics/flavonoids and one or two marker compounds) would enhance reproducibility and facilitate cross-study comparisons, particularly because extraction conditions can materially alter *C. caudatus* metabolite profiles.

Despite these constraints, the work contributes to a growing translational theme: supportive, food-derived polyphenol interventions may help address underrecognized metabolic sequelae of chemotherapy that intersect with cardiovascular risk in survivorship. Moving forward, studies that (i) include both sexes, (ii) incorporate mechanistic readouts spanning liver–heart metabolic crosstalk, and (iii) test post-exposure (strictly therapeutic) initiation alongside concurrent dosing would clarify when and how *C. caudatus* is most beneficial. Finally, because anthracycline therapy is delivered in the context of complex clinical regimens, careful attention to potential herb-drug interactions and to preserving antitumor efficacy will be essential before contemplating clinical translation.

CONCLUSION

In conclusion, doxorubicin exposure was associated with an unfavorable serum lipid profile in female Wistar rats, and administration of ethanolic *C. caudatus* extract (200 mg/kg) was linked to an overall shift toward a less atherogenic lipoprotein pattern. These findings support the potential utility of *C. caudatus* as a botanical adjunct to attenuate chemotherapy-associated dyslipidemia during anthracycline treatment. Further studies with larger cohorts, standardized phytochemical profiling, and mechanistic validation, alongside evaluation of safety and potential interactions with anticancer efficacy, are warranted to clarify translational relevance.

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