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Research Paper

Therapeutic Effects of *Cordia myxa*-Derived Zinc Oxide Nanocomposite on the Doxorubicin-Induced Hepatosplenic Histopathology in a Murine Model

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ABSTRACT

Background: Doxorubicin (DOX), a strong antineoplastic agent, has been linked to remarkable dose-limiting hepatotoxicity and splenic injury. *Cordia myxa,* a medicinal plant, has been investigated for its organ-protective and antioxidant properties and offers potential as a potential antidote. Nanoparticle-mediated delivery may improve therapeutic efficacy. This research aimed to determine the therapeutic capability of a zinc oxide-derived nano formulation of *Cordia myxa* extract against liver and spleen damage in albino mice caused by the DOX-induced histopathology

Methods: The six cohorts (n=8) comprised 48 male albino mice. Distilled water was administered to the control group. The experimental groups were administered either the nano-extract (5 or 10 mg/kg), DOX (0.12 mg/kg), or a mixture of these for a duration of 30 days. The splenic and hepatic tissues were subjected to histopathological analysis after the treatment through the Eosin (H&E) and Hematoxylin staining.

Results: The group subjected to only DOX demonstrated significant hepatic architectural derangement, including binucleation and hepatocyte atrophy, as well as distinct splenic congestion and red pulp expansion. In contrast, subjects administered nano-extract demonstrated normal tissue histology. Simultaneous nano-extract administration, especially at a 10 mg/kg dose, markedly reduced these pathological alterations, preserving near-normal hepatic integrity and diminishing splenic changes.

Conclusion: The nano formulation of *Cordia myxa* offers significant defense against DOX-induced histopathological injuries in the spleen and liver. The results indicate its potential use, as it can aid in improving the organ toxicity that has been linked to chemotherapy.

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Introduction

Doxorubicin (DOX) has been clinically utilized and has been the foundation of multiple chemotherapeutic programs for hematologic and solid malignancies since it was first identified in 1963, and has often been hindered due to its dose-dependent hepatotoxicity and cardiotoxicity [1, 2]. Approximately 30% of patients who have undergone DOX therapy have encountered hepatic injury, a result of its metabolism caused by carbonyl reductase enzymes and hepatic cytochrome P450 [3, 4]. The resultant histopathological symptoms, which involved sinusoidal congestion, hepatocellular necrosis, and inflammatory cell infiltration, were the consequences of the underlying molecular pathology, which was significantly caused by the overproduction of reactive oxygen species (ROS) and subsequent apoptosis, which was induced by oxidative stress [5–7].

Natural products have emerged as a potential field to find an approach that could reduce the toxicity induced by chemotherapy [8]. *Cordia myxa L.*, a member of the Boraginaceae family, is a medicinal plant that has established traditional medicine systems globally [9]. The diverse and abundant phytochemical profile is responsible for its therapeutic potential, which involves a broad range of flavonoids (such as rutin, quercetin, robinin), alkaloids, phenolic acids (such as chlorogenic acids and caffeic acids), and other bioactive compounds [10, 11]. *C. myxa* has demonstrated immunomodulatory activities and hepatoprotective properties and has significantly contributed to its strong antioxidant activity [12].

Recently, advanced nanotechnology has offered an innovative solution to reduce natural restrictions in phototherapeutics, which include low bioavailability, poor solubility, and rapid metabolism [13, 14]. The materials have been engineered at the nanoscale (1–100 nm), potentially producing advanced drug delivery systems that could improve the target-specificity and biological activity of the plant-derived compounds [15]. The studies have frequently indicated that nano-encapsulated plant extracts demonstrated significant hepatoprotective effects in comparison to their crude analog, which frequently achieved significant or equivalent efficacy at considerably lower rates of doses [16, 17].

This study was designed to study the protective efficacy of a nano-extract of *Cordia myxa* against the organ damage induced by DOX. The hepatoprotective properties of *C. myxa* and the improved bioavailability yielded by nano-formulation [18]. The well-known albino mouse model of chemotoxicity was utilized; the study aimed to explain the potential of a nano-herbal approach to improve histopathological alterations in splenic and hepatic tissues, which can provide a potential adjuvant therapy to improve the risk assessment of anthracycline-based chemotherapy.

Materials and Methods

Plant Material and Extraction

Dried fruits of *Cordia myxa* were purchased from a local market in Babylon, Iraq, and authenticated by a botanist at the Department of Biology, University of Babylon. A voucher specimen (CM-2023-01) has been deposited in the university herbarium. For the preparation of the aqueous extract, 10 g of pulverized fruit material was suspended in 100 mL of distilled water. The suspension was agitated at ambient temperature for 2 hours, followed by filtration through Whatman No. 1 filter paper. The resulting filtrate was clarified by centrifugation at 4500 rpm for 15 minutes, and the supernatant was collected and stored at 4°C for subsequent use [19, 20].

Synthesis and Characterization of Cordia myxa Zinc Oxide Nano-Extract

The synthesis of zinc oxide nanoparticles (ZnO-NPs) was accomplished via a green chemistry approach, utilizing the aqueous C. myxa extract as a bioreducing and capping agent, based on a modified protocol from El-Beltagi et al [21]. A total of 0.2 M zinc acetate dihydrate solution was added dropwise to 100 mL of the aqueous extract under continuous magnetic stirring. Subsequently, the pH of the reaction mixture was adjusted to 12 with the addition of 1 M sodium hydroxide (NaOH) and kept at 60°C for 3 hours. The distinct color change indicated the formation of a precipitate, demonstrating a high yield of ZnO-NPs. Centrifugation was utilized to harvest the nanoparticles at 4500 rpm for a duration of 15 minutes, which was subsequently washed thrice with distilled water for purification and was kept in an oven at 40–45°C to let it dry. The final product underwent milling and was converted into a fine powder to produce a nanosuspension.

Characterization of Cordia myxa Zinc Oxide Nano-Extract

Particle size distribution and surface charge

Dynamic Light Scattering (DLS) was utilized to assess the polydispersity index (PDI), hydrodynamic size, and zeta potential of the synthesized ZnO-NPs

Morphology

The Scanning Electron Microscopy (SEM) was utilized to determine the surface morphology of the ZnO-NPs.

Purity and crystalline structure

X-ray Diffraction (XRD) was used to determine the crystalline structure of ZnO-NPs, and energy-dispersive X-ray (EDX) analysis was used to examine the elemental composition of the ZnO-NPs.

Stability

Changes in zeta potential and particle size were monitored at 4°C for 30 days to determine the stability of the nano-formulation.

Animal Model and Husbandry

This study utilized 48 adult male albino mice (Mus musculus), aged 8-10 weeks and weighing 28–30 g. The animals were housed in polypropylene cages containing sterile wood chip bedding under controlled laboratory conditions (25 ± 2 °C, 50-60% relative humidity, 12-hour light/dark cycle). A standard commercial pellet diet and water were available ad libitum throughout the acclimatization and experimental phases.

Experimental Protocol and Dosing Regimen

Using a simple randomization scheme, the mice were allocated to one of six experimental groups (n=8 per group):

- Group 1 (Control): Received daily oral gavage of distilled water (10 mL/kg) for 30 days.
- Group 2 (DOX): Administered a single intraperitoneal (i.p.) injection of doxorubicin (0.12 mg/kg) on day 1.
- Group 3 (NE-5): Received daily oral gavage of the C. myxa nano-extract at 5 mg/kg for 30 days.
- Group 4 (NE-10): Received daily oral gavage of the C. myxa nano-extract at 10 mg/kg for 30 days.
- Group 5 (DOX + NE-5): Received (5 mg per kg, p.o., daily) nano-extract for a duration of 30 days plus a one DOX dosage (0.12 mg/kg, i.p.) on day 1.
- Group 6 (DOX + NE-10): Received (10 mg per kg, p.o., daily) nano-extract for a duration of 30 days plus a one DOX dosage (0.12 mg/kg, i.p.) on day 1.

The dose of 0.12 mg/kg was chosen to induce a mild, sub-chronic level of toxicity, allowing for a more sensitive evaluation of the protective effects of the nano-extract against low-grade, persistent organ damage, which can be more clinically relevant than acute, high-dose toxicity models. While higher doses are commonly used to induce acute hepatotoxicity [10, 22] This low-dose approach was selected to model a subtler and cumulative injury pattern.

Sample Collection and Histopathological Examination

At 24 hours following the final treatment, animals were euthanized by cervical dislocation under deep isoflurane anesthesia, in compliance with AVMA guidelines. The excision was performed on the spleen and liver; excess tissues were cleansed and settled in neutral buffered formalin of approximately 10% for a duration of 48 hours. The tissues underwent dehydration via a graded ethanol series, were cleared, embedded in paraffin wax, and sectioned to a thickness of 5 µm. Hematoxylin and Eosin (H&E) were used to stain the sections for microscopic analysis. Two independent pathologists, blinded to the group assignments,6 performed the histopathological evaluation.

Semi-Quantitative Histological Scoring

A semi-quantitative scoring system was utilized for the determination of the severity of liver and spleen injury, following the previous studies [11, 23]. Hepatocyte degeneration/necrosis, sinusoidal congestion, central vein congestion, and disruption of hepatic cord architecture were the parameters that were determined for the liver. Red pulp congestion and disruption of red-white pulp architecture were utilized for the assessment of the spleen. On a scale of 0 to 3 or 4, each of the following parameters was assessed, where 0 indicated no change and higher scores which demonstrated enhanced severity of the lesion. By the summation of the scores for all parameters, the total injury score for each organ was determined.

Statistical Analysis

The statistical analysis was performed, in which the data were presented as mean ± standard deviation (SD). The Shapiro-Wilk test was utilized to determine the normality of the data. One-way analysis of variance (ANOVA) was utilized to determine the statistical comparisons between groups for normally distributed data, which was followed by Tukey's post-hoc test. The Kruskal-Wallis test was utilized for the determination of non-normally distributed data, which was followed by Dunn's post-hoc test. A p-value was considered statistically significant if it was less than 0.05.

GraphPad Prism 9 was utilized for the determination of all statistical analyses.

Ethical Declaration

All experimental protocols involving animals were reviewed and sanctioned by the Central Bioethics Committee of the University of Babylon, under approval number 1348, dated November 14, 2023.

Results

Hepatic Tissue Analysis

The control cohort (Group 1) had microscopic examination of hepatic tissue, and Groups 3 and 4 had the mice administered the nano-extract monotherapy, which demonstrated a well-preserved parenchymal architecture. The radially arranged hepatic cords were placed around the central veins, and the normal morphology with distinct nuclei and intact cytoplasm was demonstrated by hepatocytes (Figures 1 and 2).

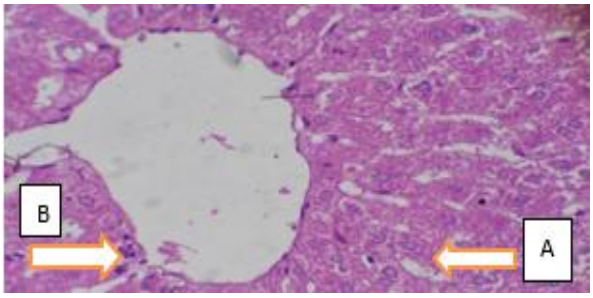

Figure 1. Representative photomicrograph of hepatic tissue from a control mouse. The image displays (A) hepatocytes with normal morphology and (B) a central vein surrounded by intact parenchyma, indicating a normal histological structure.

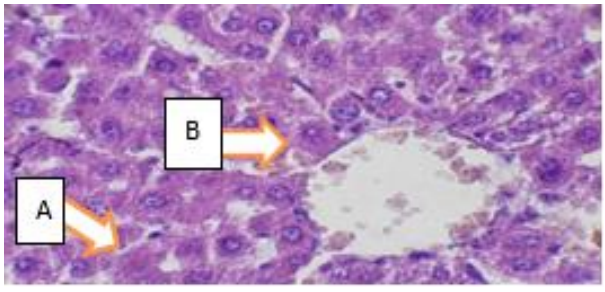

Figure 2. Liver histology of treated mouse which had high-dosage of nano-extract of *Cordia myxa* (10 mg per kg) alone. The section shows (A) normal hepatocyte arrangement and (B) an intact central vein, demonstrating the absence of toxicity from the nano-extract itself. (H&E, 400X magnification).

In contrast, Group 2, which had the DOX-only, displayed intense histopathological derangements. The widespread degeneration of the hepatocyte, cytolysis, and the appearance of binucleated cells and the normal hepatic architecture were also severely compromised. The distinct congestion of the central veins and the significant vascular disturbances were also prominent (Figure 3). The total liver injury score for this group was significantly higher than that of the control group (p<0.001) and was determined by the semi-quantitative scoring (Table 1).

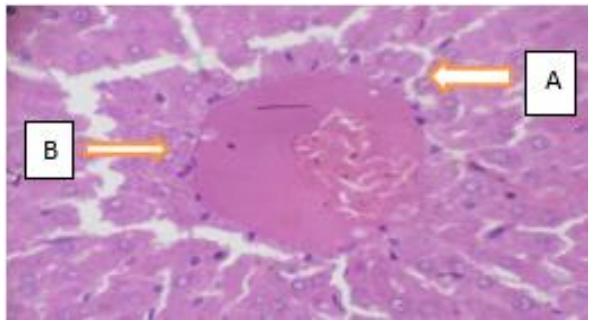

Figure 3. Photomicrograph illustrating severe doxorubicin-induced hepatotoxicity. The liver section obtained through a sole dose of DOX administered to a mouse (0.12 mg per kg, i.p.) shows (A, arrow) extensive histopathological damage, such as hepatic atrophy and disarray of cell, and (B, arrow) pronounced congestion. (Hematoxylin & Eosin, magnification 400x).

The *Cordia myxa* nano-extract, which was administered to the co-treatment cohorts, gave significant protection against hepatotoxicity induced by DOX. Group 5, DOX + NE-5, which was administered with the lower dose of the nano-extract, had a highly preserved hepatic structure, with mild congestion, and only the focal areas of hepatocyte necrosis were observed, as shown in Figure 4.

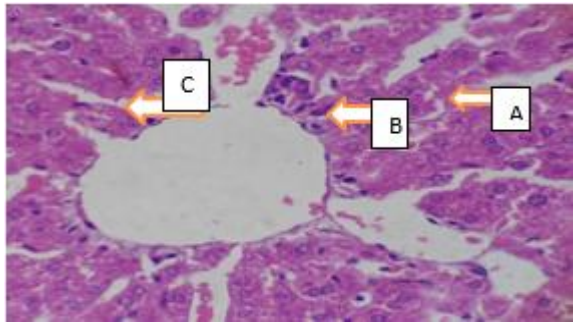

Figure 4. Photomicrograph illustrating severe doxorubicin-induced hepatotoxicity. The liver section obtained through a sole dose of DOX administered to a mouse (0.12 mg per kg, i.p.) shows (A, arrow) extensive histopathological damage, such as hepatic atrophy and disarray of cell, and (B, arrow) pronounced congestion. (Hematoxylin & Eosin, magnification 400x).

Group 6, DOX + NE-10, which was administered with high-dose and was a co-treatment group, had a powerful protective effect (Figure 5). Here, the minor cytological variations, which included slight changes in hepatocyte size and minimal sinusoidal dilation, were observed along with the liver tissue being completely

Table 1. The semi-quantitative histological assessment for liver injury.

Group	Hepatocyte Degeneration (0-4)	Sinusoidal Congestion (0-4)	Central Vein Congestion (0-3)	Hepatic Cord Disruption (0-3)	Total Score
Control	0.1 ± 0.2^{a}	0.2 ± 0.3^{a}	0.1 ± 0.2^{a}	0.1 ± 0.2^{a}	0.5 ± 0.6^{a}
DOX	3.5 ± 0.5^{c}	3.2 ± 0.4^{c}	2.8 ± 0.4^{c}	2.7 ± 0.5^{c}	12.2 ± 1.5^{c}
NE-5	0.2 ± 0.3^{a}	0.3 ± 0.4^{a}	0.2 ± 0.3^{a}	0.2 ± 0.3^{a}	0.9 ± 0.8^{a}
NE-10	0.1 ± 0.2^{a}	0.2 ± 0.3^{a}	0.1 ± 0.2^{a}	0.1 ± 0.2^{a}	0.5 ± 0.5^{a}
DOX + NE-5	1.5 ± 0.5^{b}	1.2 ± 0.4^{b}	1.1 ± 0.3^{b}	1.0 ± 0.4^{b}	4.8 ± 1.2^{b}
DOX + NE-10	0.8 ± 0.4^{ab}	0.7 ± 0.3^{ab}	0.6 ± 0.3^{ab}	0.5 ± 0.3^{ab}	2.6 ± 0.9^{ab}

Data are presented as mean ± SD (n=8). Values with different superscript letters (a, b, c) are significantly different ($p < 0.05$).

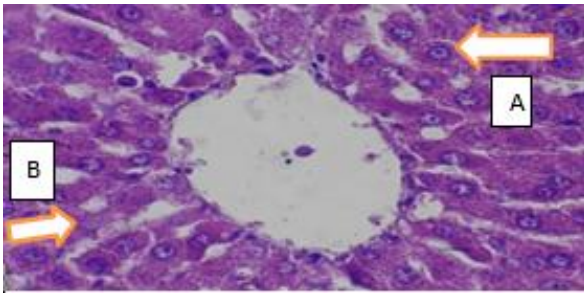

Figure 5. Evidence of significant protection against doxorubicin-induced damage in a mouse from the high-dose co-treatment group (10 mg/kg nano-extract and 0.12 mg per kg DOX). Liver tissues exhibited a typical histology, with (A) conserved hepatic cords only (B) mild dilation of liver sinusoids. (Hematoxylin & Eosin, magnification 400x).

protected from the injury, as shown in Figure 5. As compared to the DOX-only group, the total injury scores for both co-treatment groups were substantially decreased ($p < 0.001$). Specifically, as compared to the 5 mg/kg dose, the 10 mg/kg dose demonstrated a statistically significant protective effect ($p < 0.05$) (Table 1).

Splenic Tissue Analysis

In control, Group 1 had the splenic microarchitecture) Groups 3 and 4 had a nano-extract-only, which was normal, and characterized by the distinct red pulp (splenic cords and sinusoids) and the demarcated white pulp (lymphoid follicles) as shown in Figures 6 and 7, respectively.

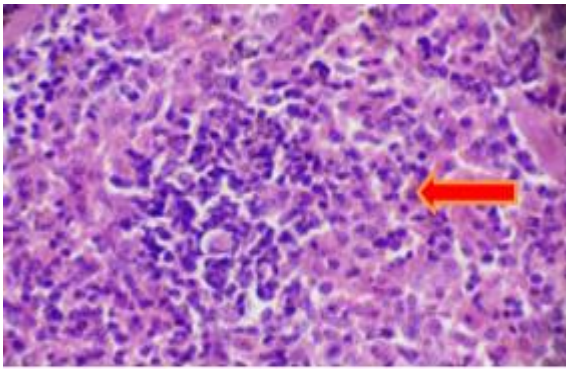

Figure 6. Typical splenic microanatomy from a control mouse. The section shows the typical appearance and distribution of white and red pulp. (Hematoxylin & Eosin, magnification 400x).

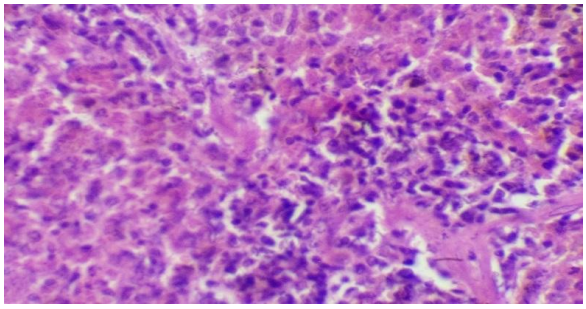

Figure 7. Histology of spleen from a mouse administered the high-dose Cordia myxa nano-extract (10 mg/kg) as a monotherapy. The image confirms the biocompatibility of the nano-extract, showing a preserved microarchitecture of the red and white pulp with no discernible pathological changes. (H&E, 400X magnification).

Conversely, Group 2 was the DOX-treated group, whose spleens demonstrated significant pathological changes. The most evident finding involved a significant expansion of the red pulp and intense vascular congestion, which, as a result, led to an effacement of the normal architectural boundary between the white and the red pulp regions, as shown in Figure 8. Consequently, compared to the control group, the total spleen injury score was significantly elevated in the DOX group ($p < 0.001$), as shown in

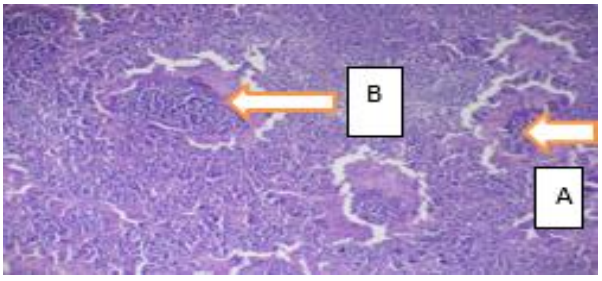

Figure 8. Severe splenic pathology following a single dosage of doxorubicin (0.12 mg per kg). Photomicrograph reveals (A) marked vascular congestion and (B) a significant expansion of the red pulp, leading to the effacement of the normal splenic architecture. (H&E, 100X magnification).

Table 2.

The nano-extract was administered concurrently with DOX, resulting in a significant improvement in these splenic lesions. Group 5, DOX + NE-5, was the low-dose co-treatment group; only modest histological deviations from the norm were demonstrated in the

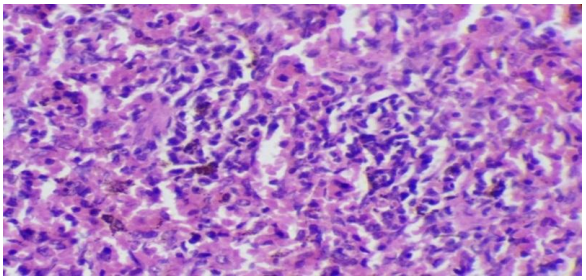

Figure 9. Amelioration of doxorubicin-induced splenic injury by the low-dose Cordia myxa nano-extract. This spleen section from a co-treated mouse (5 mg/kg nano-extract and 0.12 mg/kg DOX) demonstrates a significant reduction in pathological changes, with only minor architectural alterations visible. (Hematoxylin & Eosin, magnification 400x).

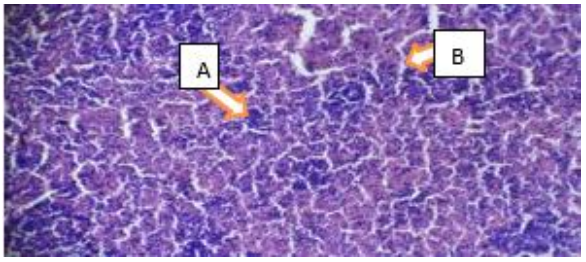

Figure 10. Robust splenoprotective outcome of the high-dosage of nano-extract of Cordia *myxa*. The co-treated mouse with the high-dosage of nano-extract (10 mg per kg) as well as DOX (0.12 mg per kg), the spleen shows only mild histopathological findings, such as (A) minimal red pulp alteration and (B) slight hemorrhage, with the overall architecture remaining largely intact. (H&E, 400X magnification).

Table 2. Semi-quantitative histological scores for spleen injury.

Group	Red Pulp Congestion (0-3)	Red-White Pulp Architecture (0-3)	Total Score (0-6)
Control	0.2 ± 0.3^{a}	0.1 ± 0.2^{a}	0.3 ± 0.4^{a}
DOX	2.8 ± 0.4^{c}	2.6 ± 0.5^{c}	5.4 ± 0.8^{c}
NE-5	0.3 ± 0.4^{a}	0.2 ± 0.3^{a}	0.5 ± 0.6^{a}
NE-10	0.2 ± 0.3^{a}	0.1 ± 0.2^{a}	0.3 ± 0.4^{a}
DOX + NE-5	1.2 ± 0.4^{b}	1.0 ± 0.4^{b}	2.2 ± 0.7^{b}
DOX + NE-10	0.7 ± 0.3^{ab}	0.6 ± 0.3^{ab}	1.3 ± 0.5^{ab}

Data are presented as mean ± SD (n=8). Values with different superscript letters (a, b, c) are significantly different ($p < 0.05$).

spleen when compared to the significant damage exhibited in the DOX-only group, as shown in Figure 9. Group 6, DOX + NE-10, had a distinct protective effect compared to the high-dose group; only minimal red pulp alterations and symptoms of hemorrhage were demonstrated by the spleen. Crucially, the fundamental organization of the spleen, including the clear segregation of red and white pulp, was preserved (Figure 10). The total injury scores for both co-treatment groups were significantly lower than those of the DOX-only group ($p < 0.001$) (Table 2).

Discussion

The present study provides compelling histopathological evidence that a novel zinc oxide-based nano-extract of Cordia myxa significantly mitigates doxorubicin-induced hepatic and splenic injury in a murine model. The severe tissue damage observed in the animals treated solely with DOX corroborates the well-established organotoxic profile of this widely used anthracycline. The observed pathological changes, including disruption of hepatic cord architecture, extensive hepatocyte degeneration, and vascular congestion, are in strong agreement with previous reports on DOX-induced liver injury and are reflective of the underlying pathophysiology [23], which is primarily driven by the generation of reactive oxygen species (ROS) during hepatic drug metabolism [24].

Binucleated hepatocytes were the characteristic cellular response to genotoxic stress, indicating impaired cytokinesis followed by DNA damage. The results aligned with the established DOX mechanism, which included an inhibition of topoisomerase I and in intercalation into DNA, as a result which triggered an apoptotic cell death [9]. Moreover, central vein congestion, also known as pronounced vascular alterations, emphasized the harmful effect of the drug on the hepatic microcirculation, as this finding aligned with the comprehensive knowledge of its cellular-level effects [25].

The co-administration of the *C. myxa* nano-extract was outstanding and had a dose-dependent protective effect as compared to the severe damage in the DOX-only group. The enhanced bioavailability and stability of the ZnO nanoparticle delivery system were evident at the 10 mg/kg dose, which had superior efficacy. The inherent limitations of the traditional herbal extracts were successfully conquered by the nanomedicine approach, which involved rapid degradation and poor solubility; as a result, the delivery of bioactive constituents to the target tissues was improved [26]. The absence of any pathological alterations in the groups that were treated with the nano-extract alone demonstrated the exceptional biocompatibility of the formulation, which was a critical observation that could be for its potential clinical translation [27].

The *C. myxa* nano-extract had a therapeutic action that was mediated by its abundant phytochemical composition, especially its enhanced concentration of phenolic acids and flavonoids. These compounds exhibited strong antioxidant properties, resulting in a direct counteraction of the oxidative stress induced by DOX. The current study emphasized the histological results, which significantly indicated that the protective mechanism involved the collection of free radicals and upregulation of an endogenous antioxidant defense. The previous studies have demonstrated that by upregulating enzymes such as SOD, catalase, and GPx, *Cordia myxa* extracts can restore redox homeostasis [28, 29]. The direct ROS scavenging and prevention of lipid peroxidation can be utilized for the protection of rich flavonoid and phenolic content [30]. Future studies should involve biochemical assays to determine antioxidant enzyme activity and oxidative stress markers, to confirm this hypothesis.

The enhanced protective efficacy of the 10 mg/kg compared to the 5 mg/kg nano-extract (Groups 6 and 5) indicated a clear dose-dependent correlation. Both doses provided significant protection compared to doxorubicin alone; however, the elevated dose resulted in near-complete preservation of architecture, with minimal alterations, including mild sinusoidal dilatation and occasional slight variations in hepatocyte size. The complete architectural preservation with a 10 mg/kg dose was obtained as a result of the protective efficacy of the nano-extract, which could be optimized by the dose-dependent response. The protective mechanisms remained unchanged at therapeutic concentrations, as minimal histological alterations were found in the high-dosage treatment group, which further reinforced the safety profile of the nano formulation [31, 32]. The groups that received only nano extract (such as Groups 3 and 4) showed no toxic effects, indicating a therapeutic range and supporting the future potential for clinical use of these dosages.

The nano-extract also indicated a significant ability to preserve splenic architecture, in addition to its hepatoprotective effects. This finding is significant, as it indicates a systemic protective action. The preservation of distinct red and white pulp regions found in the co-treated animals demonstrated a reduction in immune system suppression and a modulation of the inflammatory cascade [28]. Immune surveillance and hematopoiesis were crucial for preserving splenic function, emphasizing the comprehensive therapeutic potential of this formulation, which can be essential for preserving immune integrity during chemotherapy. Nevertheless, to translate these preclinical histological outcomes into substantial clinical advantages, future functional immunological studies and clinical trials are required [33, 34].

The *C. myxa* extract can be utilized as a carrier for the application of ZnO NPs, resulting in a significant step toward potential phytopharmaceutical agents in the delivery system. Nanotechnology enhances their stability, cellular uptake, and target delivery, overcoming the natural shortfall that has negatively limited the clinical development of plant-derived therapeutics [26]. Green synthesis of nanoparticles using plants provides eco-friendly and medical benefits [21]. The dose-dependent therapeutic response, which was confirmed in this study, could be crucial for optimizing treatment schedules and future clinical translation. The potential for therapeutic effects at reduced dosages (5 to 10 mg/kg), compared with normal plant extracts, may reduce side effects and facilitate patient compliance in clinical use.

Limitations of the study

While this investigation provides strong evidence for the protective effects of the C. myxa nano-extract, certain limitations should be acknowledged. The study utilized an acute, single-dose model of DOX toxicity, which may not completely summarize the cumulative organ damage that can be observed in chronic chemotherapy regimens. Future studies should use multi-dose models to determine the long-term protective efficiency. Moreover, without direct biochemical and molecular data, the comprehension of the underlying mechanisms remains hypothetical. Future research should include quantitative analyses of oxidative stress markers, liver function (e.g., ALT, AST), and the molecular pathways involved (e.g., Nrf2 signaling) to demonstrate an in-depth understanding of the protective mechanisms. Before considering clinical trials, the results from this study should be validated in other preclinical models as a critical step for the clinical trial.

Conclusion

This study provided a nanotechnology-enhanced formulation of *Cordia myxa,* which offered remarkable, dose-dependent protection against hepatosplenic damage induced by doxorubicin in mice. The combination of conventional herbal medicine along with a modern nanodelivery system, this formulation provides a potential approach for the development of an adjuvant therapy to reduce the organ toxicity that has been linked to chemotherapy. Further research is warranted to fully elucidate the mechanisms of action and to evaluate the clinical potential of this novel nano-herbal therapeutic.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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