



Comparative Efficacy of Coriander Seed Extract-Loaded Selenium Nanoparticles and DMSA in Restoring Antioxidant/Apoptotic Balance of Lead-Induced Hepatotoxicity

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Abstract

Lead (Pb) is a heavy metal that causes hepatotoxicity even in trace amounts. This study investigated the therapeutic potential of coriander extract-loaded selenium nanoparticles (coriander@Se-NPs) against Pb toxicity in a mouse model, comparing its efficacy to the benchmark standard chelator, DMSA. The effectiveness of coriander extract, coriander@Se-NPs, and synthetic chelator (DMSA) was evaluated. The study groups contain: a control group receiving distilled water, a Pb toxicity group given Pb-acetate at 150 mg/kg, a positive control group treated with DMSA after Pb exposure, and two groups receiving coriander extract or coriander@Se-NPs after Pb exposure, both at 200 mg/kg daily for three weeks. Our results demonstrated that the coriander@Se-NPs significantly reduced hepatic Pb concentrations (83.90%) and restored antioxidant enzyme activities (SOD and CAT) more effectively than DMSA. Notably, coriander@Se-NPs exhibited potent anti-inflammatory and anti-apoptotic effects, evidenced by a 12.5-fold reduction in IL-6 and the suppression of Caspase 3 to sub-normal levels (0.399-fold). Furthermore, the coriander@Se-NPs treatment stabilized Beclin 1 levels, suggesting a restoration of cellular autophagy homeostasis. These findings indicate that coriander@Se-NPs provide a superior, multi-modal protective shield against heavy metal poisoning compared to traditional synthetic chelators, DMSA, highlighting their potential as a high-efficacy nanomedicine for clinical toxicology. Further studies are needed to explore its potential clinical applications and mechanisms.

Keywords Coriander extract · Selenium nanoparticle · DMSA, Beclin 1 · BCL-2

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Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
BSA	Bovine serum albumin
Casp-3	Caspase 3
CV	Central vein
IL-6	Interleukin 6
ROS	Reactive oxygen species
Se	Selenium
Se-NPs	Selenium nanoparticles
SOD	Superoxide dismutase

Introduction

Lead (Pb) is a heavy metal frequently found in paints. It contaminates the soil and is taken up by plants, leading to various harmful effects on living organisms when ingested [1]. Pb toxicity, even at low levels, can affect cognitive abilities, causing lower IQ, and hyperactivity in young children. Also, Pb toxicity can disrupt red blood cell formation, leading to anemia [2, 3]. Prolonged exposure to Pb may cause liver damage and different forms of cancer [4, 5]. Therefore, examining methods for prevention and treatment will assist us in addressing health concerns associated with Pb toxicity [6]. Chelation therapy is essential for removing Pb from water and the human body to improve health outcomes [7]. Some botanical extracts have been suggested to reduce Pb absorption and enhance the body's natural detoxification mechanisms. The use of *Coriandrum sativum* leaf powder has garnered attention as a potential chelator for heavy metals, with a soup reportedly aiding in the elimination of mercury following the removal of dental amalgams, and it remains popular despite the lack of extensive scientific support [8]. In vivo studies demonstrated that the extract from *Coriandrum sativum* seeds decreased the absorption of Pb in the bones and liver, while also enhancing Pb elimination through the kidneys [9–11]. Furthermore, a synergistic combination of coriander seed extract with vitamin E has been shown to inhibit liver damage in mice, restoring normal liver histology and reducing markers of oxidative stress compared to each component alone [12].

Selenium is an essential trace element that is vital for biological functions, particularly in protecting against oxidative damage to DNA and cells. Research shows that selenium supplementation can reduce Pb toxicity by enhancing antioxidant defenses or competing with Pb for binding sites on enzymes and proteins [13, 14]. Nanotechnology has emerged as a promising complementary avenue to mitigate Pb toxicity when certain metals and loaded natural extracts are formulated onto carrier nanoparticles [15]. Nevertheless, selenium has a limited safety range [16]. Selenium

nanoparticles (Se-NPs) exhibit significantly lower toxicity, enhanced bioavailability, and improved selenoprotein activity. Additionally, Se-NPs act as an eco-friendly selenium supplement that can help alleviate the toxic effects of heavy metals by effectively scavenging reactive oxygen species (ROS), enhancing basal metabolism, and regulating calcium balance [17, 18]. Another study found that the neuroprotective, anti-apoptotic, and anti-inflammatory effects of Se-NPs may be attributed to their ability to increase antioxidant enzymes, which neutralize excessive ROS generated by aluminum exposure [19]. Moreover, loading various natural extracts onto Se-NPs not only enhanced the antioxidant activities of Se-NPs [20], but also improved their ability to remove or chelate heavy metals and protect vital organs. Among these Se-NPs' nano-formulations, beta-cyclodextrin-graphene oxide nanoparticles loaded with Se-NPs have been shown to act as an anticancer agent by inducing apoptosis in human glioblastoma cells [21, 22]. Another study demonstrated that nano-formulation of Se-NPs with tragacanth gum, which serves as a reducing agent in their green synthesis, significantly increased both apoptotic and anticancer activities of the resultant nanocomposite against colon cancer cells compared to each component alone [23]. Beyond oncology, hesperidin's protective effect was enhanced when it was loaded onto Se-NPs stabilized with chitosan, therapy providing protection against glutamate-induced cytotoxicity in PC12 cells [24]. Similarly, the formulation of diosmin with selenium-chitosan nanoparticles alleviates glutamate-induced cytotoxicity in PC12 cells [25]. In the in vitro model of Parkinson's disease, the antioxidant and apoptotic activities of free thymol were enhanced after being formulated with Se-NPs, providing protection to SH-SY5Y cells from 6-hydroxydopamine toxicity compared to free thymol [26]. Furthermore, recent studies have highlighted the synergistic antioxidant effects of Se-NPs loaded garlic and coated with tocopherol polyethylene glycol-succinate, which demonstrated effectiveness against Pb-induced toxicity in animal models [27].

In this study, we hypothesize that loading an ethanolic extract of coriander seeds onto selenium nanoparticles will enhance the extract's ability to chelate Pb from aqueous media and facilitate Pb removal from the body. To test our hypothesis, we first synthesized Se-NPs using the ethanolic extract of coriander seeds and characterized them.

The primary focus of this study is the green synthesis of Se-NPs in the coriander seed extract with a dual-functional nano-formulation, in which Se-NPs can act as a nanocarrier to enhance the antioxidant, anti-inflammatory, and anti-apoptotic properties of coriander seed extract. Previous research has not explored this nano-formulation or tested it against Pb toxicity in animal models. Additionally, none have directly compared the formulated compounds with

the clinical standard lead chelator, DMSA. This study will implement a comprehensive approach to assess hepatic lead clearance, antioxidant enzyme activity, inflammatory cytokines, as well as markers of apoptosis and autophagy. This entire study represents a novel contribution to the existing body of research. Therefore, we will assess the safety of the nano-formulation through a chronic toxicity study. We will also use this nano-formulation in the treatment of a mouse model of Pb toxicity to evaluate its effectiveness as a hepatoprotective supplement. Furthermore, we will measure the levels of antioxidant enzymes, inflammatory cytokine (IL-6), apoptotic proteins (Bax and caspase 3), and autophagy protein (Beclin-1) in the liver homogenate of the treated animal groups.

Materials and Methods

Chemicals and Kits

Lead acetate (99%, CAS NO. 6080-56-4, BATCH NO. 2145) was maintained by the Alfa Chemical Group, Cairo, Egypt. Sodium selenite 99% (CAS#: 10102-18-8, Catalog No. SLS4189) and ascorbic acid 99.5% (CAS#: 50-81-7, Catalog No. SLA1306) were purchased from LANXESS Energizing Chemistry, www.lanxess.com, Pvt. Ltd., Thane, Maharashtra, India. DMSA (meso-2,3-dimercaptosuccinic acid) 98% (CAS: 304-55-2, Catalog No. 226670050) was purchased from ACROS Organics Company (Thermo Fisher Scientific), USA. Serum alanine aminotransferase (ALT, REF 1001171) and aspartate aminotransferase (AST, REF 1001161), albumin (ALB, REF 1001023), and creatinine (REF 1001111) kits were purchased from SPIN-REACT Diagnostics, Sant Esteve d'en Bas, Girona, Spain. Catalase (Catalog No. 502521) and superoxide dismutase (SOD, Catalog No. 502521)) were obtained from Biodiagnostic, Giza, Egypt. Mouse Bax ELISA Kit (Catalog No. ab233624) was purchased from Abcam, Cambridge, UK. www.abcam.com, Mouse Caspase 3 (Casp-3) ELISA Kit (Catalog No. CSB-E08858m) was purchased from CUSA-BIO TECHNOLOGY LLC, Houston, TX, USA, and Mouse Beclin 1 (BECN-1) Competitive ELISA kit (Catalog Number: MBS724152) was purchased from MyBioSource.com, Inc., San Diego, CA, USA. All other chemicals used were of analytical grade.

Selenium Nanoparticle Preparation

Selenium nanoparticles (Se-NPs) synthesis was established by utilizing ascorbic acid as a reducing agent, as described in previous research [28].

Extraction

The *Coriandrum sativum* seeds were obtained from a private herbalist and were identified by a botanical specialist. The seeds were carefully washed with distilled water to remove any dirt, and cracked seeds were discarded. They were then dried in an oven (Binder) at 35 °C for two days. The dried seeds were ground into a powder using a mortar. To extract bioactive compounds, maceration was employed. A total of 200 g of dried coriander seed powder was soaked in 857 mL of 70% ethanol and left at room temperature for three days, with periodic stirring to help diffusion. After three days, the mixture was filtered through a chiffon filter and a glass funnel to remove solids. The filtrate was then placed in an oven at 40 °C for two days to evaporate the bulk of the solvent and reduce the filtrate volume, a faster and more economical approach that produced the extract. The final concentrated thick extract was frozen, then freeze-dried at -20 °C to preserve the polyphenolic component of the extract from further heating, to prepare fine powdered material suitable for subsequent use in preparations [29].

Synthesis of Selenium Nanoparticles in Coriander Seed Extract (Coriander@Se-NP)

Coriander@Se-NPs were synthesized by reducing sodium selenite using coriander ethanolic extract instead of ascorbic acid. In a conical flask, 0.250 g of coriander extract powder were dissolved in 100 mL of distilled water to form a clear solution, then sodium selenite solution (0.519 g, 5 mL of distilled water) was added gradually to the mixture while stirring vigorously. The synthesis of the Coriander@Se-NPs can be observed by the change in the color of the reactant solution to deep red, which was left stirring overnight [30]. The final product was subjected to centrifugation for 10 min at 12,000 rpm in a cold centrifuge, and the resulting pellets were collected and rinsed twice with distilled water. The purified pellet was deep-frozen at -60 °C before lyophilization to preserve nanoparticle morphology, size, and dispersion during freeze-drying. It was then lyophilized at -60 °C using a freeze-dryer and stored in an airtight Eppendorf tube.

Characterization Tools

The characterization of Coriander@Se-NPs was evaluated using Field Emission Scanning Electron Microscopy (FE-SEM), JEOL model JSM-IT 100, with image processing carried out through SEM/JSM 5000 software, alongside UV-vis spectroscopy utilizing the Jasco V-770 UV Visible Absorbance Spectrophotometer. The Zeta Potential was measured by Brookhaven with a Zeta Nano Sizer for Zeta

Potential analysis. Fourier Transform Infrared Spectroscopy (FTIR) was conducted using a JASCO, Tokyo, Japan, model number AUP1200343, to identify the surface molecular structures within the range of 500–4000 cm^{-1} through the KBr pellet method.

Experimental Animals

The research involved ten-week-old male albino mice weighing between 35 and 40 g, which were bred in the animal facility at the Chemistry Department, Faculty of Science, Kafrelsheikh University. The mice were housed in clear polypropylene cages with stainless-steel mesh and kept at a temperature of 27 ± 2 °C while being exposed to a 12-hour light/dark cycle. They had free access to standard pellets and fresh water. The experiment was approved (RC. 27.3.2025) in accordance with the guidelines established by the Research Animals Ethics Committee, Benha University.

LD₅₀ Study

Male albino mice that had fasted overnight were weighed and then randomly divided into five groups of four animals each. The doses of Coriander@Se-NPs (0.1, 0.2, 0.4, 0.8, and 2 g/kg), suspended in distilled water, were administered orally as a single dose to the five groups. After a physical examination of the animals, mortality was monitored over three days.

Chronic Toxicity Study

A total of 8 mice were used in the subacute toxicity assessment, categorized into 2 groups (healthy and treated). Each mouse in the treated group was administered an oral dose of 100 mg/kg body weight of Coriander@Se-NPs (1/20 of the LD₅₀), which was suspended in distilled water, daily for a period of 28 days. The healthy group of mice received distilled water every day for 28 days. At the end of the experiment, the mice were anesthetized using an injection of ketamine and xylazine. Blood samples were taken through heart puncture, and serum was separated by centrifugation and stored at -20 °C for subsequent biochemical analysis. Livers were collected from each animal, washed with saline, and fixed with 10% formalin for histopathology.

In Vivo Pb Toxicity Mouse Model

A fresh Pb acetate solution was prepared in sterile distilled water. This solution was administered orally at a dose of 150 mg per kg/body weight daily for two weeks. Twenty-five adult male mice were randomly assigned to five groups, with five mice in each group. The healthy control group

(**Control group**) was given distilled water orally daily for three weeks. The lead acetate induction group (**Lead toxicity group**) received a dose of lead acetate at 150 mg/kg, mixed with distilled water, for the same period. The third group of mice (**Positive control group**) was first given Pb acetate (150 mg/kg of body weight) and then, after a three-hour interval, received DMSA orally at a dosage of 100 mg/kg of body weight, dissolved in distilled water, daily for three weeks [31]. The fourth group of mice (**Coriander extract treated group**) was first given Pb acetate (150 mg/kg of body weight) and then, after a three-hour interval, received coriander extract orally at a dosage of 200 mg/kg of body weight, dissolved in distilled water, daily for three weeks [32]. The fifth group (**Coriander@Se-NPs-treated**) received Pb acetate (150 mg/kg of body weight) and, after three hours, was administered the coriander@Se-NPs orally at a dosage of 200 mg/kg of body weight, also dissolved in distilled water, daily for three weeks. At the end of the study period, all animals were anesthetized using xylazine and ketamine. Blood samples were collected through cardiac puncture into heparin tubes and then centrifuged at 4000 rpm for ten minutes to separate the plasma. All plasma samples were stored at -20 °C until further analysis. The livers were carefully excised and rinsed with sterile saline, then dried on filter paper. One portion was fixed in 10% formalin for histopathological examinations, while the other two portions were weighed and frozen at -20 °C for Pb level detection and ELISA testing.

Detection of Pb Levels by Atomic Absorption

A weight of 100 mg of liver samples from each mouse was individually mixed with 1 ml of nitric acid and 0.5 ml of perchloric acid, then heated [33]. The digested tissues were analysed using a PerkinElmer PinAAcle 500 atomic absorption spectrometer, and the Pb levels were calculated as follows:

$$\text{Pb } (\mu\text{g/g tissue}) = \frac{C \times V}{W} \times 100$$

Where C=Pb concentration (mg/L), V=Final volume of digested sample, W=weight of tissue, and 100 is the factor expressed per 100 mg tissue.

Every tissue sample was analysed in triplicate, and then the averages were recorded.

Biochemical Markers

Serum parameters (ALT, AST, albumin, and creatinine) were measured following the guidelines provided in the

kits. The activities of antioxidant enzymes (catalase and SOD) in the liver tissue homogenate were assessed according to the manufacturer's specifications. Additionally, the levels of Bax, caspase 3, and IL-6 in the liver homogenate were determined using the ELISA technique, in accordance with the kit guidelines.

Statistical Analysis

The data are presented as means $\pm$ standard error of the mean (SEM). All analyses were conducted using Minitab 18 software. Results were evaluated using one-way analysis of variance (ANOVA), and comparisons between groups were made using Tukey's test. A P-value of less than 0.05 was deemed statistically significant.

Results

Particle Size, Zeta Potential of Se-NPs, and Coriander@Se-NPs

According to Fig. 1A, the mean particle sizes of Se-NPs and coriander@Se-NPs were 66 nm and 129 nm, respectively. We evaluated the uniformity of the particle size distributions using PDI. Se-NPs and coriander@Se-NPs had PDI values of 0.23 and 0.31, respectively, indicating that the particles were uniformly distributed. According to a prior study, the nanoparticles are stable and homogeneous if the PDI value is less than 0.7 [34]. Zeta potentials for coriander@Se-NPs were -30 mV (Fig. 1B). According to the suggested zeta potential values, which fall between $+30$ and -30 mV, the system might be stable. The stability of the zeta potential values is influenced by the ionic strength of the dispersion media. Coriander@Se-NPs have a negative charge due to their negative zeta potential molecules. Instead of clumping together, the nanoparticles can spread out due to the small negative value. Stability and electrostatic repulsion are enhanced by larger negative values [35].

FTIR Spectrum and Ultraviolet-Visible Spectroscopy (UV-Vis) Analysis

Figure 1c presents the FTIR spectrum of coriander extract, selenium nanoparticles (Se-NPs), and coriander@Se-NPs. A broad band at 3458 cm^{-1} is observed, associated with the O-H stretching vibrations of proteins and polyphenols found in coriander. Peaks at 2919 cm^{-1} and 2841 cm^{-1} correspond to the stretching vibrations of the CH_2 group. A peak at 1635 cm^{-1} is attributed to the stretching vibrations of the $\text{C}=\text{C}$ group. A small fringe around 1451 cm^{-1} relates to carboxylic acid (COOH) groups, indicating twisting and

bond-stretching vibrations. Finally, a peak at 746 cm^{-1} corresponds to the stretching of the C-H bond characteristic of essential oils [36]. In the spectrum of Se-NPs, a broad peak at 3424 cm^{-1} is associated with O-H stretching in alcohols and phenols. Absorption peaks at 2934 cm^{-1} and 2856 cm^{-1} are due to the C-H stretching in alkynes. The band at 1630 cm^{-1} corresponds to the N-O asymmetric stretch in nitro compounds. A strong band at 1460 cm^{-1} relates to the C-C stretching in aromatic rings. The sharp peak at 1373 cm^{-1} is attributed to C-H bending in alkanes, while the peak at 1072 cm^{-1} corresponds to C-N stretching in amines [37]. When coriander is loaded onto Se-NPs, there are noticeable changes in the intensity of peaks for both Se-NPs and coriander, with some peaks disappearing. This confirms the successful loading of coriander onto Se-NPs, forming coriander@Se-NPs.

Figure 1d & e illustrates the UV-visible spectra of coriander, Se-NPs, and coriander@Se-NPs. The coriander displays two characteristic absorption peaks at 265 nm and 329 nm, which are associated with the $\pi-\pi^*$ transition of C-C bonds and the $n-\pi^*$ transition of C-O bonds (Fig. 1d) [38]. The Se-NPs show a strong absorption peak between 250 nm and 280 nm, with a maximum at 264 nm (Fig. 1e) [39]. When coriander is loaded onto the Se-NPs to create coriander@Se-NPs, new peaks emerge, and the intensity of certain existing peaks increases slightly, indicating successful loading of coriander onto the Se-NPs (Fig. 1e).

SEM of the Se-NPs and Coriander@Se-NPs

The SEM image was captured to investigate the morphological characteristics of Se-NPs. Previous studies have shown that the SEM images of Se-NPs typically exhibit a spherical and bulky shape [40–44], which is the most common form (Fig. 1f). The reduction and nucleation of the reduced atoms during the process lead to grain coalescence. This phenomenon is attributed to the presence of various functional groups, such as lignin, which binds and nucleates selenium ions in ascorbic acid [45]. When coriander was incorporated into the Se-NPs, the resulting nanoparticles, referred to as coriander@Se-NPs, displayed a marked loss of sphericity, forming irregular, aggregated, and amorphous structures (Fig. 1g). The rough and wrinkled surface of the coriander@Se-NPs indicated the incorporation of the coriander extract onto the pores of the Se-NPs, forming a flake-shaped organic layer. However, the coriander@Se-NPs surface still has some porosity, in some regions, which may enhance their catalytic characteristics. These surface features suggested successful loading of the coriander extract onto the Se-NPs surface that changed from spherical shape to an aggregated rough assembly (Fig. 1f & g).

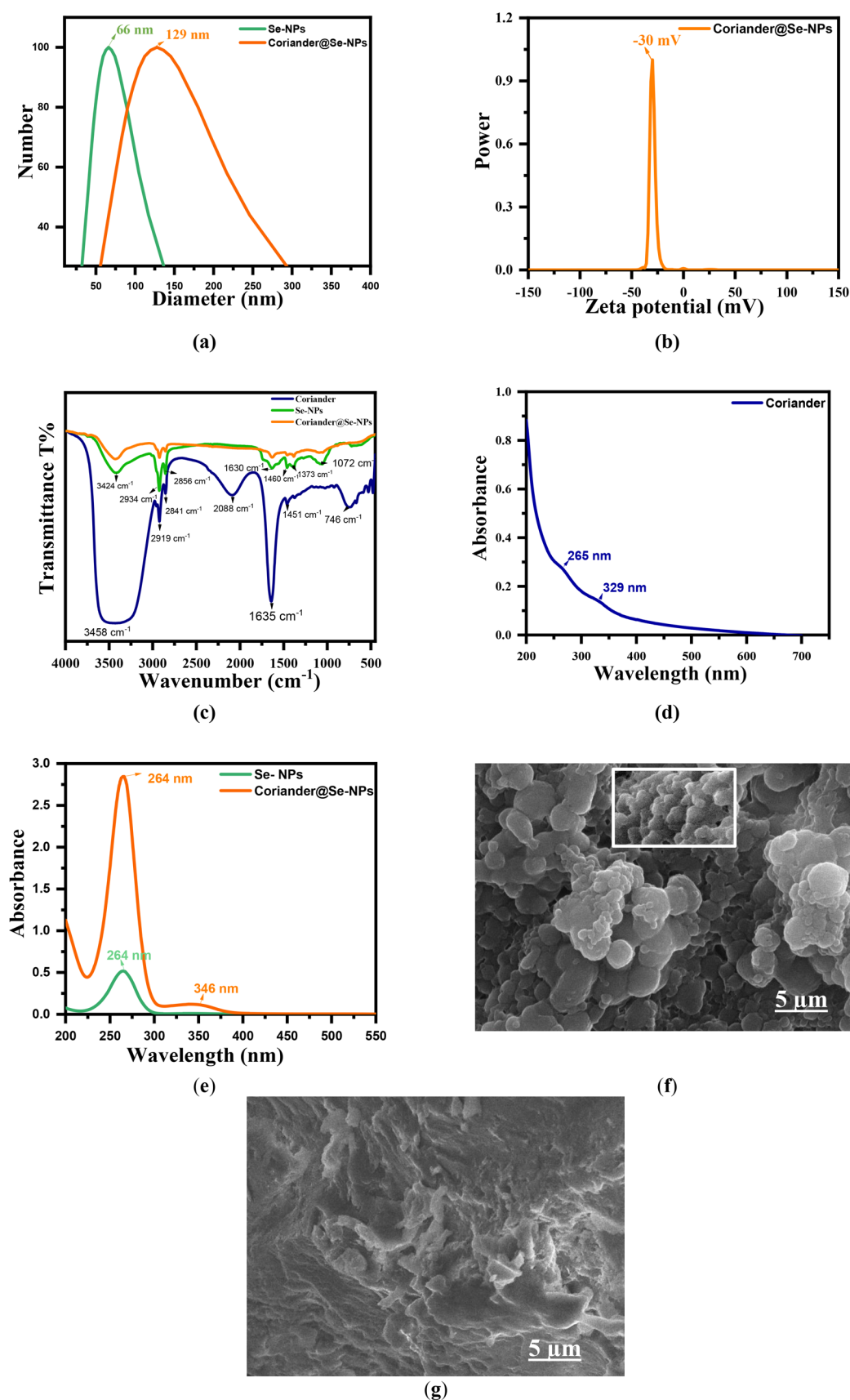


Fig. 1 (a) Particle size; (b) zeta potential of Se-NPs and coriander@Se-NPs; (c) FTIR spectra of coriander extract, Se-NPs, and coriander@Se-NPs; UV spectra for (d) coriander extract, and (e) Se-NPs and coriander@Se-NPs; (f) SEM image of Se-NPs, and (g) coriander@Se-NPs

LD₅₀ Values

A single oral dose of coriander@Se-NPs demonstrated a lethal dose (LD₅₀) higher than 2 g/kg body weight. As a result, the chosen experimental doses were 200 mg/kg body weight for the coriander@Se-NPs (which corresponds to 1/10 of the LD₅₀), and 200 mg/kg body weight for the coriander extract [32], which was mixed with distilled water.

Coriander@Se-NPs Chronic Toxicity Study

In the chronic toxicity study, two groups of mice (each consisting of four mice) received either coriander@Se-NPs at a dose of 200 mg/kg body weight suspended in 400 µL of distilled water over 28 days. The results showed no significant change in body weight after treatment compared to before treatment in either group. Additionally, there were no notable differences in the percentage change in body weight between the groups. Moreover, liver function tests revealed no significant differences between the groups. Finally, no histopathological changes were observed in the coriander@Se-NPs-treated group compared to the healthy control group (supplementary Table S1 and Figures S1 and S2).

Animal Experiment

Hepatotoxicity's Biochemical Parameters

Lead exposure has a major negative consequence of liver toxicity, since the liver acts as a main storage site for heavy metals [46]. It is crucial to explore natural and protective substances that can mitigate or change the harmful effects of lead. Plant-derived natural remedies have become a part of primary healthcare systems in developing countries [47]. Coriander seeds are known for their wide range of benefits, including their antioxidants, anti-inflammatory, hypolipidemic, and hepatoprotective effects. The hepatoprotective properties attributed to coriander seed extract are due to flavonoid glycosides, phenolic compounds, caffeic and ferulic acid, which play a role in these protective effects [48–50]. Se-NPs exhibit encouraging hepatoprotective properties, providing defense against a range of liver injuries and disorders. Research indicates that Se-NPs can lessen the harm inflicted by hepatotoxins and diminish the adverse effects of anticancer medications [51]. In particular, Se-NPs are capable of neutralizing detrimental free radicals, boosting the activity of antioxidant enzymes, and enhancing the overall redox balance in the liver [52, 53]. Furthermore, several researches proven that green-synthesized Se-NPs using plant extracts have been shown to alleviate Pb-induced hepatotoxicity in animal models [27, 53–55]. Liver enzymes (ALT and AST) are intracellular enzymes

that are elevated during liver injury and released into the bloodstream, indicating that damage has occurred [56]. In our study, we compared the treatment with coriander extract and coriander@Se-NPs with the benchmark Pb-chelation drug, DMSA. DMSA action was established to chelate Pb in the plasma, as it is water-soluble and effectively withdraws Pb from vital organs like the liver [57]. Our findings show markedly elevated liver function tests (ALT and AST), along with a significant decrease in albumin levels in the Pb-toxicity group when compared to the healthy control, positive control, coriander extract, and coriander@Se-NPs-treated groups ($p = 0.0001$ for all) (Fig. 2). After treatment with coriander extract or coriander@Se-NPs, ALT and AST activities were significantly reduced compared to the lead toxicity group, returning to normal control values. Also, no significant change in ALT and AST activities was observed between the positive control group and coriander extract- or coriander@Se-NPs-treated groups. In contrast, a notable reduction in albumin levels was seen in the Pb-toxicity group compared to the control and the three treated groups (Fig. 2). However, there were no significant changes in creatinine levels in the control and three treated groups compared with the Pb-toxicity group. These results illustrate the hepatoprotective effects of coriander extract, coriander@Se-NPs, and DMSA treatment (positive control group) against lead-induced liver injury.

Lead Levels in Animals' Liver

Pb levels in the liver samples of all animal groups were detected by atomic absorption [33]. Our data showed a significant increase in Pb levels in the liver tissues of Pb-toxicity animals compared to the control group, positive control, coriander extract, and coriander@Se-NPs ($p = 0.0001$ for all). The Pb burden was reduced by 71.94% in the positive control, 76.79% in coriander extract, and 83.90% in coriander@Se-NPs compared to the Pb-toxicity group, with no significant difference in Pb levels among the positive control, coriander extract, and coriander@Se-NPs treated groups.

Effect of Coriander@Se-NPs Treatment on Antioxidant Enzymes

SOD and catalase enzymes play vital roles in protecting against the overproduction of ROS and oxidative stress [58, 59]. SOD enzymes are especially recognized for their function in neutralizing superoxide anions by transforming them into hydrogen peroxide and oxygen. This process is then followed by catalase, an essential enzyme that converts hydrogen peroxide into water and oxygen [60]. Certain plant extracts rich in polyphenols and flavonoids can enhance the

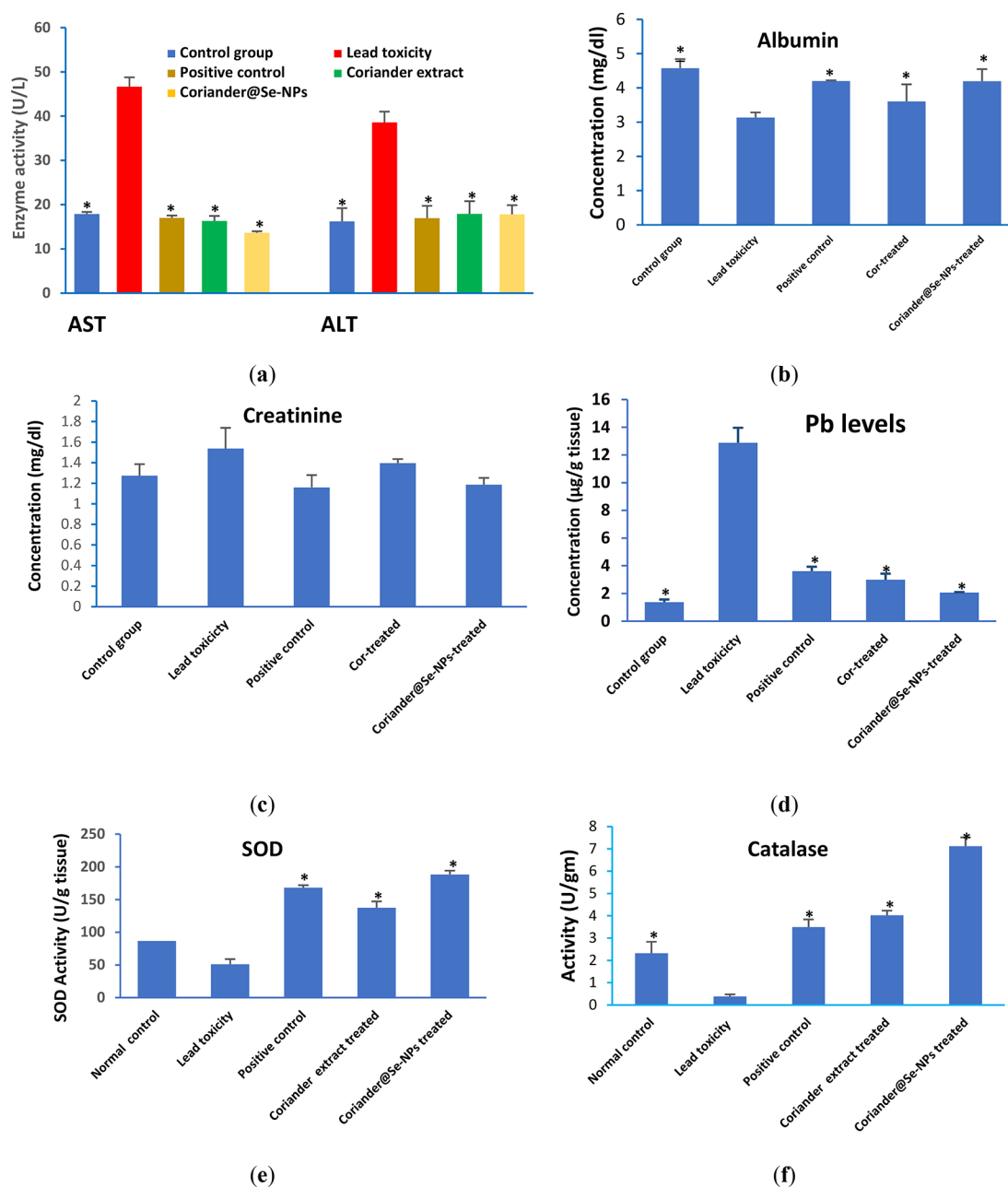


Fig. 2 Serum liver enzymes (a and b) and kidney function (creatinine (c)) levels. Pb levels in liver tissues (d). SOD (e), and catalase (f) activities in the control group, positive control, the coriander extract-

treated, and the coriander@Se-NPs-treated groups compared to the Pb-toxicity group. * Significant compared to the Pb-toxicity group

activity of the SOD and catalase enzymes [61, 62]. Figure 2e & f illustrates a notable reduction in hepatocyte SOD ($p = 0.04$) and catalase activities ($p = 0.008$) within the Pb-toxicity group when compared to the healthy control group. Furthermore, there was a considerable increase in hepatocyte SOD activity in the positive control ($p = 0.0001$), the coriander extract ($p = 0.004$) group, and the coriander@Se-NPs treated groups ($p = 0.001$) compared to the Pb-toxicity group. There was an increase of 229.87% in the positive control group, 169.52% in the coriander extract group, and

269.48% in the coriander@Se-NPs treated groups when compared to the Pb toxicity group. Importantly, hepatocyte SOD activities in the positive control ($p = 0.037$), the coriander extract ($p = 0.049$), and the coriander@Se-NPs treated ($p = 0.001$) groups were significantly higher than those of the healthy control group. There was no significant difference between the healthy control group and the Pb toxicity group ($p = 0.625$); however, SOD activities decreased by 69.85% in the Pb toxicity group compared to the healthy control group. Additionally, no significant change in the

hepatocyte SOD levels between the coriander@Se-NPs-treated group and both the positive control and the coriander extract-treated group (Fig. 2e).

Our data revealed a massive decrease in the hepatocyte catalase activity in the Pb-toxicity group compared to the healthy control group ($p=0.003$). Furthermore, the hepatocyte catalase activity showed a significant increase in the positive control (by 807.72%), the coriander extract (by 944.46%), and the coriander@Se-NPs groups (by 1750.39%) compared to the Pb-toxicity group ($p=0.0001$ for all). In contrast, the hepatocyte catalase activities in the positive control ($p=0.05$), the coriander extract ($p=0.008$), and the coriander@Se-NPs treated ($p=0.02$) groups were significantly higher than those in the healthy control group. This data revealed that the hepatocyte catalase activity in the coriander@Se-NPs-treated group was significantly greater than that of the positive control and coriander extract-treated group ($p=0.0001$ for both, Fig. 2f), confirming that the nano-formulation demonstrates enhanced antioxidant activity compared to the crude extract as well as the synthetic chelator. Moreover, lipid peroxidation in the hepatocytes of Pb-toxicity affected animals was indicated by significantly increased MDA levels (131.61 ± 8.33 nmol/g tissue) when compared to the control (24.28 ± 2.75 nmol/g tissue), positive control (23.65 ± 5.17 nmol/g tissue), the coriander extract-treated (32.92 ± 4.36 nmol/g tissue) or coriander@Se-NPs-treated (23.23 ± 2.43 nmol/g tissue) animal groups ($p=0.0001$ for all). In contrast, MDA levels in the positive control, coriander extract-treated, and coriander@Se-NPs-treated groups were significantly decreased to align with control group levels, showing no significant difference compared to the control group. However, there was no significant difference noted in the MDA levels between the positive control and coriander extract or the coriander@Se-NPs groups. These findings suggest the effectiveness of both coriander extract and coriander@Se-NPs treatments in eliminating excess ROS and improving the liver's antioxidant system during Pb toxicity.

Anti-Inflammatory Effect of Coriander Extract and Coriander@Se-NPs

In our study, we observed significantly elevated levels of IL-6 in the hepatocyte homogenate of the Pb toxicity group, showing an approximately 18-fold increase compared to the normal control group ($p=0.0001$, Fig. 3a). Treatment with either coriander extract or coriander@Se-NPs significantly reduced IL-6 levels ($p=0.0001$ for both) in the hepatocyte homogenate compared to the Pb toxicity group. Notably, treatment with coriander@Se-NPs had restored the IL-6 levels to near-normal values, resulting in a 1.47-fold increase compared to the normal group, though this change

was not statistically significant. While treatment with the positive control only managed to reduce IL-6 levels to an 8.02-fold elevation above the normal baseline, the coriander extract showed better efficacy, reducing these levels to 3.34-fold higher than the normal control. Most significantly, the coriander@Se-NPs outperformed both, bringing IL-6 levels down to a near-normal state of only 1.47-fold of the control group. Moreover, the coriander@Se-NPs treatment showed reduced IL-6 levels by 91.86%, which is significantly higher than the positive control (55.66%) and the coriander extract (81.51%). These findings suggest that coriander@Se-NPs treatment may more effectively regulate the inflammatory response induced by Pb toxicity by reducing IL-6 levels, thereby preventing liver injury better than the coriander extract.

Impact of Treatment on Bax, Beclin 1, and Caspase 3 Protein Levels

Figure 3 shows significant elevations in the protein levels of Bax ($p=0.0001$) and caspase 3 ($p=0.031$) in the hepatocyte homogenates of animals exposed to Pb toxicity compared to the normal control group. These elevations were significantly reversed by treatment with either coriander extract or coriander@Se-NPs when compared to both the Pb toxicity and normal control groups. In the group treated with coriander extract, the level of Bax decreased by 0.87-fold compared to the Pb toxicity group, although it remained significantly higher ($p=0.0001$) than in the normal control group by 185.29-fold. In contrast, the Bax level in the coriander@Se-NPs-treated group was decreased by 6.81-fold compared to the Pb toxicity control group, but still 31.16-fold greater than the levels observed in the normal control group (Fig. 3b). In contrast, the Bax level was significantly reduced in the positive control group (81.59%) and the coriander extract group (12.63%) compared to the Pb toxicity group. Interestingly, the coriander extract alone was relatively weak at inhibiting BAX, suggesting that the anti-apoptotic effect is primarily driven by the Se-NPs or the specific way they deliver the coriander's bioactive compounds. Furthermore, in the group treated with coriander@Se-NPs, the level of caspase 3 decreased by 0.399-fold compared to the normal control group. In contrast, the group treated with coriander extract showed a 4.46-fold increase compared to the normal control group, indicating a much lower capacity to suppress the apoptotic cascade. The positive control group also remained elevated, showing a 1.75-fold increase compared to the normal control, which was significantly higher than the coriander@Se-NPs-treated group. Notably, the level of caspase 3 was significantly lower in the coriander@Se-NPs-treated group compared to

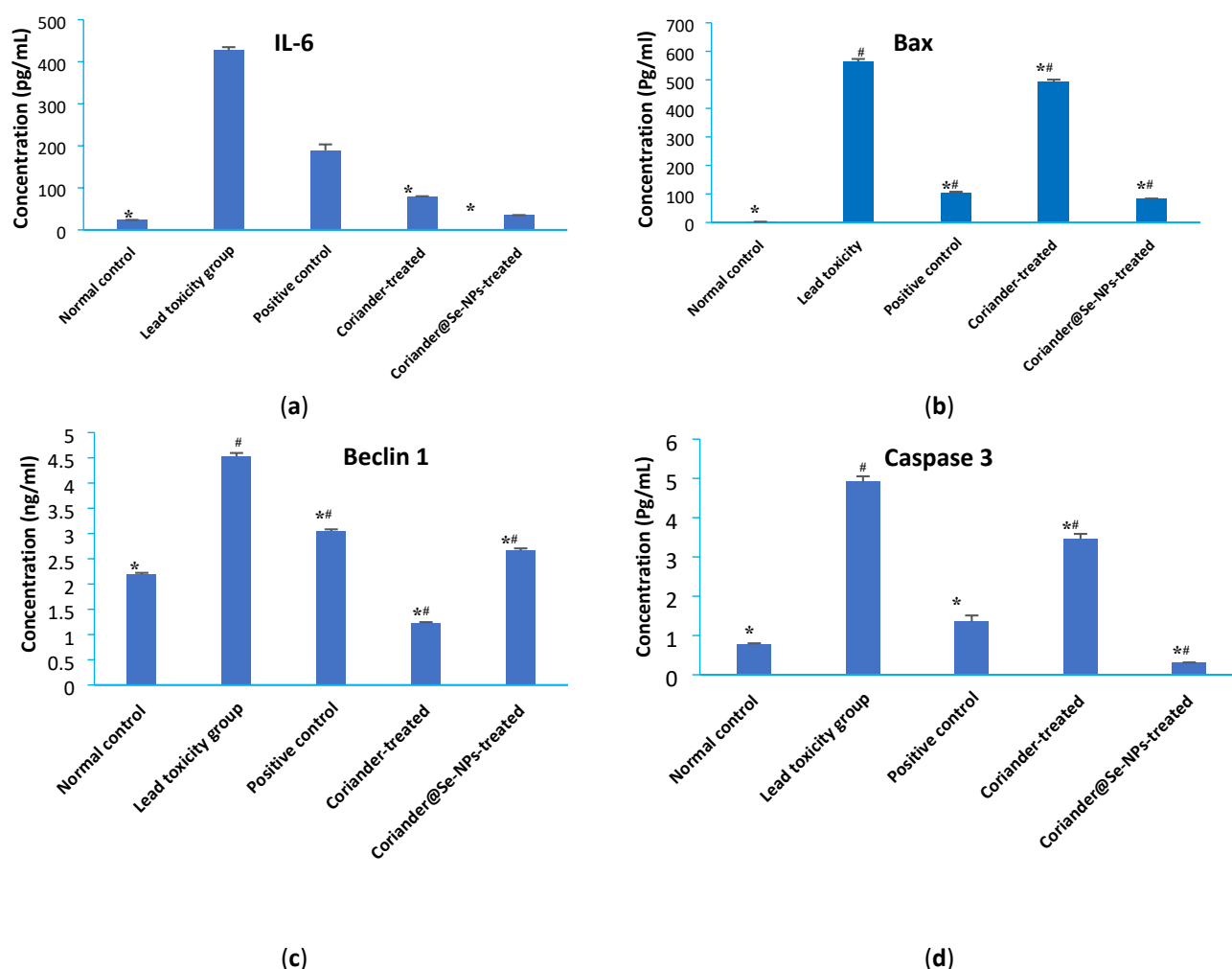


Fig. 3 (a) Bar plot represented IL-6, (b) Bax, (c) Beclin 1, and (d) caspase 3 concentrations in the hepatocyte homogenate of all study groups. * Significant compared with the Pb toxicity group ($p \leq 0.0001$), and # represents significant compared with the normal control group ($p \leq 0.0001$)

both the positive control group and the coriander extract-treated group ($p=0.0001$ for both) (Fig. 3d).

Conversely, the level of the Beclin 1 protein was significantly elevated ($p=0.0001$) in the Pb toxicity group compared to the normal control group. This elevation was reduced following treatment with DMSA (positive control group), coriander extract, or coriander@Se-NPs. In the positive control group, Beclin 1 levels were reduced by 1.48-fold compared to the Pb toxicity group, though they remained 1.39-fold higher than the normal baseline. In the group treated with coriander extract, Beclin 1 levels decreased by 3.7-fold compared to the Pb toxicity group, and by 0.565-fold compared to the normal control group. However, no significant change was observed in the coriander@Se-NPs group compared to the normal control group, although there was a 1.69-fold decrease compared to the Pb toxicity group. These data confirm the effectiveness of DMSA, coriander extract, and coriander@Se-NPs, with

superiority of both DMSA and coriander@Se-NPs in stabilizing the hepatocytes' Beclin 1 levels near normal range. These findings highlight the protective effects of coriander extract and coriander@Se-NPs against Pb toxicity, particularly in modulating apoptosis and autophagy-related proteins. Moreover, the coriander@Se-NPs exhibit a more potent protective effect against Pb toxicity by maintaining a balance in apoptosis and autophagy-related proteins. This indicates their potential as a therapeutic agent for mitigating heavy metal-induced cellular damage.

Effect of Coriander Extract and Coriander@Se-NPs on Liver Histopathology

The histopathological examination of liver samples demonstrated a notable improvement in the groups treated with DMSA, coriander extract, and coriander@Se-NPs compared to the Pb toxicity group (Fig. 4c-e). The analysis of

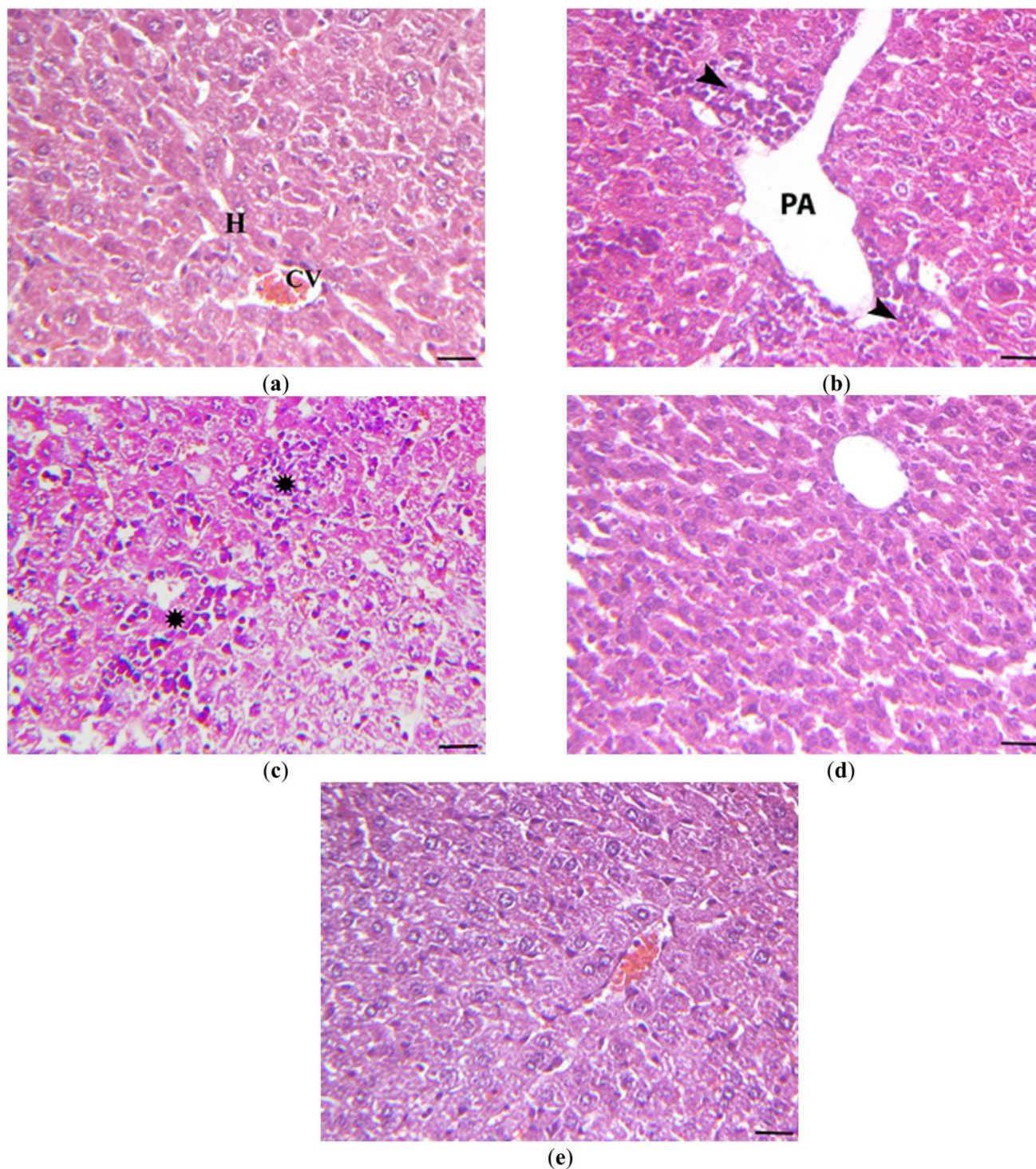


Fig. 4 Histopathological photomicrographs of the H&E-stained liver sections of normal control (a), Pb toxicity (b), positive control group (c), the coriander extract-treated (d), and the coriander@Se-NPs-

treated groups (e). H=Hepatocytes, CV=Central vein, and PA=portal area. Scale bar = 50 μ m

liver tissues from mice exposed to Pb toxicity revealed periportal hepatic necrosis with infiltration by inflammatory cells (indicated by arrowheads). Additionally, signs of hemorrhage within the hepatic parenchyma were observed,

characterized by the accumulation of extravasated red blood cells in the portal triads and sinusoids (Fig. 4b). This finding suggests potential vascular complications or acute liver injury. In contrast, liver sections from mice that received

either coriander extract or coriander@Se-NPs showed no signs of hemorrhage, and the liver structure appeared to return to normal. Furthermore, liver sections from mice that received DMSA (positive control) showed multifocal hepatic necrosis invaded with inflammatory cells (asterisk) (Fig. 4c). Our findings indicate that the oral administration of both coriander extract and coriander@Se-NPs significantly reduces liver injury caused by lead acetate; however, DMSA treatment reduces the Pb burden but does not decrease the inflammation in the hepatocytes.

Discussion

Chelators in the human body are compounds that bind minerals through two or more coordination bonds, enabling their transportation and facilitating biological functions [63, 64]. Minerals are retained in tissues through ionic bonds, as seen in skeletal minerals, or through coordination bonds, which occur with proteins like albumin and enzymes, as well as the amino acids cysteine and methionine [65]. In contrast, heavy metals such as Pb do not have any essential biochemical functions. Instead, Pb binds to tissues in various organs, leading to severe toxic effects. These effects may stem from oxidative stress, endocrine disruption, and interference with essential cations such as magnesium and zinc [66–70]. Pb competes with magnesium and zinc for binding sites on proteins and transporters, hence complicating its impact on health [71, 72]. Chronic illnesses, including cardiovascular, kidney, and liver diseases, are significantly linked to Pb exposure, even at low concentrations [73, 74]. The International Agency for Research on Cancer (IARC) classifies inorganic Pb as a probable carcinogen [75]. Several synthetic Pb chelators were used to remove the Pb burden from the body. DMSA is an approved synthetic chelator that effectively removes Pb from plasma, thereby reducing its concentration in the blood. It is water-soluble and works to withdraw Pb from vital organs, such as the liver [57].

Certain macronutrients have been proposed to decrease the absorption or reabsorption of Pb and to improve the body's natural detoxification processes. *Coriandrum sativum* leaves have caught interest as a heavy metal chelator, as a soup was claimed to promote the excretion of mercury after dental amalgam removal, and continues to be favored despite limited scientific evidence [8]. In animal studies, *Coriandrum sativum* seed extract reduced Pb absorption in bones and liver, as well as increased Pb excretion from the kidney [9–11].

Selenium is an essential trace element and micronutrient that plays a crucial role in biological processes, particularly in cellular antioxidant defense. This defense mechanism protects DNA and other cellular components from oxidative

damage. Numerous studies have confirmed that selenium administration can protect against Pb toxicity. It does this by enhancing antioxidant defenses or by competing with lead for binding sites on enzymes and proteins [13, 14]. However, selenium has a narrow safety margin [16]. Se-NPs exhibit significantly reduced toxicity, good bioavailability, and an effective enhancement of selenoproteins activity. Furthermore, Se-NPs serve as an environmentally friendly selenium supplement that can help decrease the toxic effects of heavy metals by efficiently scavenging ROS, improving basal metabolism, and maintaining calcium balance [17, 18].

In this study, we synthesized Se-NPs in the coriander seed ethanolic extract, a reducing agent, to increase the Pb chelation capability of the coriander extract. Then, we investigate the therapeutic potential of the green-synthesized Se-NPs loaded with coriander extract (coriander@Se-NPs) in mitigating Pb-induced hepatotoxicity, comparing its efficacy against both crude coriander extract and the standard synthetic chelator, DMSA (Positive control group). This study was conducted using male mice to exclude the influence of hormones found in female mice that could affect the results related to antioxidant, anti-inflammatory, and anti-apoptotic proteins. The resultant nano-formulation (coriander@Se-NPs) was irregular, aggregated, and amorphous in shape with a particle size of 129 nm. This shape allows coriander@Se-NPs to be distributed in aqueous media, enhancing their reactivity.

Our LD₅₀ results indicated that coriander@Se-NPs are safe, with a threshold exceeding 2 g/kg of body weight. Furthermore, the chronic toxicity study showed no signs of toxicity in hepatocytes, supported by normal liver function tests and histopathological evaluations of liver sections with no weight loss during the 28-day experiment. These findings indicate a need for further testing of coriander@Se-NPs as a Pb chelator in vivo, especially in comparison to the efficacy of DMSA as a benchmark Pb chelator in the Pb-toxicity mouse model. We excluded the Se-NPs group from the treated groups because several studies have demonstrated its efficacy against Pb-toxicity in animal models [27, 53, 55, 76].

In our in vivo Pb-toxicity animal model, we observed significantly elevated levels of liver function enzymes and reduced albumin levels, indicating severe liver damage due to Pb exposure. These findings align with recent studies on Pb toxicity [54]. In contrast, other Pb toxicity models did not show significant changes in liver and kidney parameters [31], which may be attributed to the higher Pb dosage used in our study. This damage was corroborated by histopathological analysis. Treatment with either DMSA, coriander extract, or coriander@Se-NPs significantly reduced liver enzyme levels and increased albumin levels, restoring these

values to those seen in the control group of normal animals. Additionally, the histopathological examination of liver sections from animals treated with coriander extract and coriander@Se-NPs showed a normal liver architecture with no signs of hemorrhage; however, the DMSA histopathological examination showed some inflammation. These data were consistent with previous research that established the hepatoprotective capability of coriander oil, leaf, or seed extracts [49, 50, 77, 78]. Pb-toxicity also affects the kidneys and central nervous system, but the current study shows that coriander@Se-NPs provide significant hepatoprotection against Pb-induced toxicity, outperforming DMSA. Pb-acetate exposure at the dose and duration used in this study did not appear to cause overt impairment of glomerular filtration, as evidenced by the lack of significant differences in serum creatinine, an indicator of renal function, among the experimental groups (Fig. 2c). Serum creatinine, on the other hand, is a very insensitive marker that usually only increases after significant glomerular slow destruction. As a result, it may miss early or subclinical renal injury, tubular dysfunction, or localized oxidative/inflammatory/apoptotic alterations within kidney tissue. Therefore, it is not appropriate to consider the nonsignificant change in creatinine as proof of complete nephroprotection. A more thorough renal evaluation would be necessary for a comprehensive comparison between coriander@Se-NPs and DMSA, since DMSA's therapeutic efficacy is examined across numerous target organs. Therefore, to fully determine the systemic therapeutic profile and clinical translatability of this nanocomposite in comparison to traditional chelation therapy, future studies should include additional, more sensitive renal markers (e.g., blood urea nitrogen, KIM-1), renal oxidative stress and apoptotic markers, histopathological evaluation, as well as neurobehavioral and neurochemical endpoints.

Pb toxicity is primarily driven by the accumulation of Pb ions in soft tissues, which disrupts cellular metabolism [79]. As expected, the synthetic chelator DMSA significantly reduced Pb concentrations (71.94% reduction). DMSA functions through its vicinal thiol groups, which form stable, water-soluble complexes with lead for renal excretion [31, 33]. However, the coriander@Se-NPs outperformed DMSA, achieving an 83.90% reduction and bringing lead levels closer to the normal baseline. This suggests that the high surface-area-to-volume ratio of the nanoparticles [59, 80, 81], combined with the natural chelating agents found in coriander (such as carboxylic acids and polyphenols), provides a more efficient "trapping" mechanism for circulating Pb ions than the synthetic standard.

Se-NPs can mitigate the harmful effects of heavy metals by decreasing ROS production, enhancing antioxidant enzymes (SOD and catalase), and boosting metabolism [51,

55]. Green synthesis of Se-NPs by using plant extracts has increased the antioxidant, anti-inflammatory, and chelating efficiency of the plant extract [76, 82, 83]. SOD and catalase are essential in protecting against oxidative stress; SOD transforms superoxide anions into hydrogen peroxide and oxygen, while catalase breaks down hydrogen peroxide into water and oxygen [61, 84, 85]. Certain plant extracts that are high in polyphenols and flavonoids replicate SOD activity, offering antioxidant benefits that may aid in the treatment of diseases associated with elevated ROS, such as toxicity from heavy metals [86, 87]. Our *in vivo* findings showed decreased levels of SOD and catalase in the hepatocyte homogenate of animals subjected to Pb toxicity. Treatment with either coriander extract or coriander@Se-NPs resulted in significant increases in both SOD and catalase levels in the hepatocyte homogenate, compared to the Pb toxicity and normal control groups, with the highest elevation observed in the groups treated with coriander@Se-NPs. While DMSA treatment recovered both SOD and catalase levels, likely by removing the Pb ions that inhibit them [88, 89], the coriander@Se-NPs triggered a far more robust response. This data supports the notion of enhanced antioxidant efficiency and ROS scavenging activity of the coriander extract when loaded onto Se-NPs. These findings align with previous studies that highlighted the superior antioxidant potency of green-synthesized Se-NPs in plant extracts [37, 54, 76, 82, 90, 91]. Moreover, Selenium delivery in nanoparticle form likely provides the necessary precursors to restore the cellular antioxidant machinery more effectively than simple Pb removal via DMSA could achieve alone.

Inflammation functions as a protective response of the immune system to external threats. The inflammatory storm and subsequent cell death are the final stages of Pb-induced organ damage. IL-6 is a key cytokine that influences inflammatory responses and supports cell survival; however, under increased exposure to stressors, IL-6 can trigger apoptosis [92]. Exposure to Pb elevates IL-6 levels, which may intensify inflammatory conditions, leading to increased cellular stress and a higher chance of apoptosis [93]. In our study, IL-6 levels were about 18-fold higher in the hepatocyte homogenate of the Pb toxicity group compared to the control. Both coriander extract and coriander@Se-NPs treatments significantly reduced IL-6 levels. Coriander@Se-NPs restored IL-6 levels close to normal with a 1.47-fold increase, while coriander extract showed a significant 3.345-fold increase. Furthermore, coriander@Se-NPs resulted in a two-fold reduction in IL-6 compared to coriander extract. When comparing the coriander@Se-NPs treatment to DMSA, it was observed that the nano-formulation was more effective in reducing inflammation than DMSA. This enhanced effect may be due to the antioxidant activity of Se-NPs, combined with the antioxidant and

anti-inflammatory properties of the components in the coriander extract. These components are delivered by the Se-NPs into the cells, where they chelate Pb, remove ROS, and protect hepatocytes from inflammatory damage. This finding indicates that coriander@Se-NPs may more effectively regulate Pb-induced inflammation and protect against liver injury compared to both coriander extract and DMSA. This data confirms that the combination of Se-NPs and coriander extract was superior in reducing inflammation by decreasing IL-6 levels than DMSA [94, 95].

Apoptosis is a programmed cell death process important for cellular restoration and stress response. It can be triggered by external factors, like Pb, or by internal factors, such as excess ROS [96]. Various genes and proteins regulate apoptosis, with the Bax protein playing a key role during ATP depletion. When ATP levels drop, Bax moves from the cytosol to the mitochondrial outer membrane, leading to dysfunction and swelling. This assembly forms pores that release cytochrome c and other pro-apoptotic factors, activating caspases and ultimately resulting in cell death [97]. Pb toxicity increases Bax protein levels in hepatocytes, leading to apoptotic cell death while inhibiting anti-apoptotic proteins. In the coriander extract group, Bax decreased 0.87-fold compared to the Pb group but remained 185.29-fold higher than the normal control. The coriander@Se-NPs group showed a 6.81-fold reduction in Bax compared to the Pb group, yet its levels were still 31.16-fold greater than in the normal control. Since coriander extract reduces Bax levels, it indicates a partial protective effect against Pb-induced toxicity, despite levels remaining elevated compared to controls. The results indicated that both coriander extract and coriander@Se-NPs help mitigate Pb-induced toxicity by lowering Bax protein levels, but the effect is notably stronger with coriander@Se-NPs. Moreover, the anti-inflammatory effect of coriander@Se-NPs is closely reflected in the apoptotic markers BAX and caspase 3. While DMSA reduced BAX levels by ~ 81%, the coriander@Se-NPs achieved a superior reduction (85.36%). It was proven that Se-NPs alleviate Pb toxicity by controlling ROS accumulation and hindering apoptosis in Pb-exposed rats [55, 98]. Most strikingly, caspase 3, the executioner protease, was suppressed by the coriander@Se-NPs to a level lower than the normal control (0.399-fold). The decreased caspase 3 could be attributed to the Se-NPs, which decreased apoptosis in Pb-induced hepatotoxicity [55]. This indicates that the Se-NPs provide a more profound anti-apoptotic effect than DMSA, which primarily focuses on metal clearance rather than regulating cellular signaling.

Autophagy plays a vital role in the creation and breakdown of cellular components, serving to dispose of unnecessary materials [99]. It is activated during developmental stages and as a response to stress or disease. Studies suggest

that suppressing autophagy makes cells more prone to apoptosis caused by starvation, whereas inhibiting apoptosis may initiate autophagic cell death [96]. Beclin-1 is critical for autophagy; its overexpression can lead to elevated levels of cytochrome c in the cytoplasm, triggering the activation of caspases-3 and -9, which can result in both apoptotic and autophagic cell death [100]. In our study, Pb toxicity elevated Beclin-1 protein levels and triggered caspase-3 activation, resulting in both apoptotic and autophagic cell death in hepatocytes [101]. In the coriander extract-treated group, Beclin 1 levels decreased by 0.565-fold compared to the normal control and by 3.7-fold compared to the Pb toxicity group. The coriander@Se-NPs group showed no significant change from the normal control, but a 1.69-fold decrease compared to Pb toxicity. Interestingly, the coriander extract caused a drastic drop in Beclin 1 to sub-normal levels, which might indicate an imbalance in cellular recycling. The coriander@Se-NPs and DMSA, however, stabilized Beclin 1 near the normal baseline. This suggests that the nano-formulation and DMSA promote a physiologic restoration of autophagy, helping the cell maintain homeostasis rather than simply shutting down the stress response. These results highlight the protective effects of both treatments against Pb toxicity, with coriander@Se-NPs demonstrating a superior ability to maintain balance in apoptosis- and autophagy-related proteins. However, our study only tested male mice, which limits the generalizability of the results to females. Hormonal differences between the sexes affect metabolism, anti-inflammatory, and antioxidant responses. For example, estrogen has established antioxidant and anti-inflammatory effects, which may protect hepatocytes from Pb toxicity and influence the study results if female mice were used. Therefore, the hepatoprotective effect of either coriander extract or coriander@Se-NPs observed in this study doesn't extend to female subjects. A comparative study between both sexes is needed in the future to determine the exact effect in each group. Moreover, future research could explore the application of this treatment in clinical settings to assess its efficacy and safety in human populations.

Conclusion

In conclusion, our research confirmed that the extract of coriander seeds loaded with selenium nanoparticles (coriander@Se-NPs) has a robust ability to scavenge ROS and shows considerable activity of SOD and catalase. Moreover, it can decrease levels of the apoptotic Bax protein while lowering the expression of Beclin 1 and caspase 3 in the hepatocytes impacted by Pb toxicity. Moreover, the treatment with coriander and Se-NPs has reduced the progression of inflammation by lowering the levels of IL-6. While

DMSA remains a functional standard for Pb chelation, its scope is largely limited to metal removal. The coriander@Se-NPs represent a superior therapeutic candidate because they combine potent chelation with active biological restoration. Therefore, the consumption of coriander seeds or their nano-formulation as a dietary supplement may offer a promising strategy to prevent hepatotoxicity caused by Pb or other heavy metals. While hepatoprotection was robustly proven, future studies must evaluate the nano-formulation's systemic efficacy (e.g., nephroprotection) to fully validate its superiority against systemic chelators like DMSA. Additionally, it can help reduce oxidative stress, thereby protecting vital organs from damage. Nevertheless, tackling Pb toxicity is a multifaceted issue; therefore, additional molecular research is necessary to investigate the mechanisms by which coriander@Se-NPs mitigate the effects of Pb toxicity.

In the present work, a dosage of 200 mg/kg/day was selected based on a toxicological study of nanoparticles and plant extracts in mice. However, this dosage cannot be directly correlated to a dose that has been validated for human use. Therefore, the current findings should be considered as preclinical proof-of-concept evidence rather than a basis for immediate clinical application. Formal allometric scaling and toxicokinetic evaluations are necessary to translate animal doses to humans, and these have not yet been conducted for this formulation. Before considering coriander@Se-NPs for therapeutic applications, it is essential to conduct higher-level animal studies, as well as pharmacokinetic and pharmacodynamic investigations. Although Se-NPs have been reported to be safer compared to selenium supplements at equivalent elemental doses, this safety profile must be confirmed for this nanocomposite through dedicated studies on safety and selenium accumulation, particularly given selenium's narrow therapeutic index.

Clinical translation will require assessing both shorter (acute poisoning) and longer (chronic exposure) therapy windows, as the three-week treatment period used here corresponds to a subacute exposure model. It is also necessary to establish formulation-related factors such as oral bioavailability, manufacturing scalability, and batch-to-batch consistency of the green-synthesis processes. At this stage, the clinical translation of coriander@Se-NPs is still in its early examination. Current research should be viewed as encouragement for further preclinical studies rather than as justification for direct human use.

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Data Availability The original contributions presented in this study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author(s).

Declarations

Ethics Approval and Consent to Participate The animal study received approval following the standards set by the Research Animals Ethics Committee at Benha University, Egypt (RC. 27.3.2025). All animal research was performed in compliance with relevant laws, regulations, and guidelines, focusing on reducing potential harm and enhancing animal welfare.

Conflict of Interests The authors declare no competing interests.

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