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Research Article
Protective Effects of Jasonia Montana-Selenium Nanoparticles Against Doxorubicin-Induced Liver Toxicity

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Abstract
Background and Objective: Doxorubicin administration induces hepatotoxicity by production of reactive oxygen species (ROS) and cytokines that result in imbalanced redox potential leading to oxidative stress and reduced levels of antioxidant enzymes. The purpose of this study was to evaluate the protective effect of Jasonia Montana aqueous extract-selenium Nanoparticles (JMAE-SeNPs) against Dox-induced liver toxicity in rats. **Materials and Methods:** JMAE-SeNPs were prepared and characterized in terms of particle size and zeta potential. Furthermore, the IC_{50} of JMAE-SeNPs against Hep-G2 liver carcinoma cell line and LD_{50} was calculated. A total of 84 adult albino rats were used to assess the liver protective activity of JMAE-SeNPs against DOX-induced liver toxicity in rats. **Results:** JMAE-SeNPs had size of around 25 nm with negative zeta potential of -36.8$\pm$0.62. Also, its IC_{50} against Hep-G2 liver carcinoma cell line and LD_{50} was equal to 166.78 µg mL^{-1} and 1120 mg kg^{-1} body weight, respectively. The daily oral administration of JMAE-SeNPs at concentrations of 1/50 LD_{50} (25 mg kg^{-1} body weight) and 1/20 LD_{50} (50 mg kg^{-1} body weight) for 30 days to rats treated with DOX (2.0 mg kg^{-1} body weight) resulted in a significant improvement in plasma ALT, AST, AST and LDH as well as liver MDA, caspase-8, TNF- κB and IL-1β. Oral administration of JMAE-SeNPs, on the other hand, increased the activity of SOD, GPx and GSH in DOX-treated rats. Furthermore, JMAE-SeNPs almost normalized these effects of DOX in liver tissue. **Conclusion:** The biochemical and histological findings of our study demonstrated that JMAE-SeNPs have liver protective activity against DOX-induced liver toxicity in rats.

Key words: Jasonia Montana, selenium nanoparticles, doxorubicin, liver toxicity, caspase-8, TNF- κB, IL-1β

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Doxorubicin (DOX) is a highly effective antitumor drug but it is limited in its use due to a dose-dependent, irreversible and progressive cardiomyopathy that can manifest after the completion of treatment[1-5]. The pathomechanism of DOX-related late cardiotoxicity is multifactorial[6,7] but according to the most accepted theory, the oxidative stress is caused by the drug's redox cycling [8,9].

DOX redox-cycling begins with a one-electron reduction, resulting in the formation of the DOX* radical[10]. NADPH cytochrome P_{450} reductase[9], NOS[11-13], NADPH oxidase[14, 15] and catalase[16] are just a few of the NADPH and NADH-dependent enzymes that catalyze this reaction.

Jasonia Montana is found in the Mediterranean[17], including the Sinai Peninsula[18]. The herb has a strong herbal odour and is traditionally used to treat diarrhoea, stomachaches and chest diseases[18].

Jasonia Montana has been found to contain polyphenols[19], mono- and sesquiterpenes[20], flavonoids[21] and essential oils[22], making it a promising potential species[23]. These polyphenols have higher antioxidant properties than vitamins C and E[24]. *In vivo* studies have been conducted to assess antioxidant[25], hypoglycemic[26], anticholestatic[27] and anti-obesity[28] activities of Jasonia Montana.

Nanoparticles can help patients with less side effects by directly treating the disease and eliminating the need for blood circulation[29,30]. As drugs are encapsulated into nanoparticles (as opposed to non-encapsulated drugs), researchers have seen improved drug solubility, regulated release, increased organic bioavailability, increased stability and better long-term storage[31]. These characteristics are promising and may be needed for disease prevention[32]. Previous studies have determined the therapeutic value of medicinal plants[21-28,32], in the present study we provided an easy route for assessing the therapeutic potential of Jasonia Montana aqueous extract-selenium Nanoparticles (JMAE-SeNPs) against doxorubicin-induced liver toxicity.

MATERIALS AND METHODS

Chemicals: Doxorubicin (DOX) was obtained from Sigma Chemical Co. (St. Louis MO, USA).

Plant material: Fresh aerial parts of Jasonia Montana were collected from the Sinai Peninsula. The plant was identified by Prof. Heba A. Elgizawy, Pharmacognosy department, Faculty of Pharmacy, October 6 University.

Preparation of aqueous extract: The aqueous extract of air-dried aerial parts was prepared by dissolving a known amount of powder of air-dried aerial parts in distilled water using a magnetic stirrer. It was then filtered and evaporated to dryness under reduced pressure. An aqueous suspension, which is used normally in folk medicine, was prepared to facilitate easy handling.

Phytochemical screening: A phytochemical analysis of aerial parts of Jasonia Montana was conducted for the detection of alkaloids, cardiac glycosides, flavonoids, tannins, anthraquinones, saponins, volatile oil, coumarins and triterpenes[33].

Synthesis of Jasonia Montana aqueous extract-Selenium Nanoparticles (JMAE-SeNPs): Only 20 mM ascorbic acid (Vc) solution was freshly prepared by dissolving 35.2 mg powder in 10 mL water. JMAE-SeNPs was dissolved in 10 mL deionized water and diluted in deionized water (90 mL) in a conical flask as follows: Dissolved selenious acid (H_2SeO_3, 0.013 g., 0.01 mmol.) in 10 mL deionized water was added to the solution, with continuous stirring and heating at 60°C for 10 h; after this, 200 µL of 40 mM ascorbic acid was added as a catalyst; the red JMAE-SeNPs were suspended and characterized by transmission electron microscopy (TEM).

JMAE-SeNPs characterization: The crystal-line characteristics and grain dimensions of JMAE-SeNPs were determined by the X-ray diffraction pattern at 25-28°C with nickel (Ni) (D8 Advance X-ray diffractometer) filtered using CuKα (β = 1.54184 A0) radiation as X-rayed source. Scanning electron microscope and field transmission microscope at an accelerating voltage of 15Kv and 200 Kv have investigated the morphology and size of the JMAE-SeNPs.

Determination of JMAE-SeNPs cytotoxicity on cells: The 96 well tissue culture plate was inoculated with 1×10^5 cells mL^{-1} (100 uL $well^{-1}$) and incubated at 37°C for 24 h to form a complete monolayer sheet. After forming a confluent sheet of cells, growth medium was decanted from 96 well micro titer plates and the cell monolayer was washed twice with wash media. Two-fold dilutions of the tested sample were made in RPMI medium with 2% serum (maintenance medium). In each well, 0.1 mL of each dilution was tested, with three wells serving as controls and receiving only maintenance medium. The plate was incubated at 37°C and then examined.

Cells were checked for any physical signs of toxicity, e.g. partial or complete loss of the monolayer, rounding, shrinkage, or cell granulation. MTT solution was prepared (5 mg mL^{-1} in PBS) (BIO BASIC CANADA INC). Only 20 uL MTT solution

were added to each well. Place on a shaking table, 150 rpm for 5 min, to thoroughly mix the MTT into the media. Incubate (37°C, 5% CO_2) for 1-5 h to allow the MTT to be metabolized. Dump off the media. (dry plate on paper towels to remove residue if necessary). Resuspend formazan (MTT metabolic product) in 200 uL DMSO. Place on a shaking table, 150 rpm for 5 min, to thoroughly mix the formazan into the solvent. Read optical density at 560 nm and subtract background at 620 nm. Optical density should be directly correlated with cell quantity.

Animals: Male albino rats weighing approximately 150±10 g (84 rats; 60 for LD_{50} estimation and 24 rats for estimation of JMAE-SeNPs liver protective activity) were obtained from the animal house of Cairo University, Giza, Egypt. At the National Cancer Institute Animal House, they were housed in plastic cages with stainless steel covers. In a light-controlled room, the animals were kept at a temperature of 21±2°C and a humidity of 55-60%. The animals were kept for one week to acclimate and standard feed and water were given *ad-libitum*.

Determination of LD_{50} of JMAE-SeNPs: Preliminary tests were performed on groups of four rats. JMAE-SeNPs were administered orally in various doses to determine the range of doses that cause zero to 100% mortality in animals. The LD_{50} was determined in groups of ten animals by administering resveratrol nanoemulsion at different doses of 500, 750, 1000, 1250, 1500 and 1750 mg kg^{-1} orally. Animals were observed individually every hour for the first day and every day for the next five days following administration of the tested JMAE-SeNPs. Throughout the experiment, animals' behaviour and clinical symptoms were recorded. Finney's[34] method was used to calculate the LD_{50} using the following equation:

$$LD_{50} = Dm\left[\frac{\sum(Z \times d)}{n}\right]$$

Dm : The largest that kill all animals
∑ : The sum of (z×d)
Z : Mean of dead animals between 2 successive groups
d : The constant factor between 2 successive doses
n : Number of animals in each group

Experimental setup and ethics approval: This experiment was carried out to examine the protective effect of JMAE-SeNPs against DOX-induced liver toxicity. This experiment was conducted in accordance with guidelines established by the Animal Care and Use Committee of October 6th University.

The Research Ethics Committee at the Faculty of Applied Medical Sciences, October 6 University in Egypt, granted ethical approval for data collection (No. 20201202). There were no human subjects used in the studies that served as the foundation for this research; instead, rats were used in an *in-vivo* study. Adult albino rats were divided into four groups with six animals in each. The treatment groups are described in Table 1.

After 30 days of treatment, blood samples were drawn from each animal's retro-orbital vein and collected in heparin-containing tubes. The heparinized blood samples were centrifuged for 20 min at 1000×g. The separated plasma was used to calculate the transaminases (L-alanine and L-aspartate)[36], alkaline phosphatase (ALP)[37] and LDH[38] activity.

II-Preparation of liver samples: Animals were euthanized by cervical dislocation and then the liver was quickly removed. To prepare a 25 percent W/V homogenate, a portion of each liver was weighed and homogenized in a glass homogenizer (Universal Lab. Aid MPW-309, mechanika precyzyjna, Poland) with ice-cold saline. Three aliquots of the homogenate were prepared. The first was deproteinized with ice-cold 12% trichloroacetic acid and the supernatant obtained after centrifugation at 1000 xg was used to calculate GSH.

The second aliquot was centrifuged at 1000 xg and the supernatant was used to calculate the levels of MDA, caspase-8, necrosis factor-κB (NF-κB) and interleukin-1β (IL-1β). The third aliquot of homogenate was used to prepare a cytosolic fraction of the liver by centrifuging it at 10500 xg for 15 min at 4°C in a cooling ultra-centrifuge (Sorvall comiplus T-880, Du Pont, USA) and the clear supernatant (cytosolic fraction) was used to determine the activities of SOD and GPx using rat ELISA kit. The test was conducted based on the supplier's protocol (Rapid, Bio. Laboratories, Inc.).

Histological assessment: The liver was cut into pieces and fixed in a 10% buffered formaldehyde solution for histological

Table 1: Description of treatment groups

Groups	Group name	Treatment description
I	Normal control A	3 mL of distilled water, orally for 30 days
II	DOX	Subcutaneous injection of 2.0 mg kg^{-1} body weight DOX[35] once a week for four weeks
III	JMAE-SeNPs+DOX	Oral suspension of 1/50 LD50 (22.4 mg kg^{-1} body weight JMAE-SeNPs) in water+subcutaneous injection of 2.0 mg kg^{-1} body weight DOX once a week for four weeks
IV	JMAE-SeNPs+DOX	Oral suspension of 1/20 LD50 (56 mg kg^{-1} body weight JMAE-SeNPs) in water+subcutaneous injection of 2.0 mg kg^{-1} body weight DOX once a week for four weeks

study. An automated tissue processing machine was used to process the fixed tissues. Tissues were embedded in paraffin wax using standard techniques. Sections of 5 lm thickness were prepared and stained with hematoxylin and eosin for light microscopy analysis using the Bancroft and Steven method[39]. Following that, the sections were examined under the microscope for histopathological changes and photomicrographs were taken.

Statistical analysis: The results were expressed as Mean±SD. SPSS/18 Software was used to perform statistical analysis[40]. Data were analyzed using one-way analysis of variance followed by the least significant difference test with a significance level of 5%.

RESULTS

TEM analysis showed that JMAE-SeNPs had size of around 25 nm with negative zeta potential of -36.8±0.62 (Fig. 1). Figure 2(a and b) shows that the IC_{50} of JMAE-SeNPs against Hep-G2 liver carcinoma cell line was 166.78 µg mL^{-1}.

Table 2 shows that oral administration of JMAE-SeNPs at different doses of 500, 750, 1000, 1250, 1500 and 1750 mg kg^{-1} body weight resulted in mortalities of 0, 2, 3, 7, 8 and 10 rats, respectively. The dose of JMAE-SeNPs that killed half of the rats (LD_{50}) was 1120 mg kg^{-1} body weight.

Table 3 shows plasma ALT, AST, ALP and LDH activity. Intraperitoneal administration of DOX (2.0 mg kg^{-1} body weight) significantly increased the ALT, AST, ALP and LDH activity as compared to the control group (p<0.05), indicating acute liver toxicity. Treatment of animals with JMAE-SeNPs at the dose of 22.4 and 56 mg kg^{-1} body weight, significantly reduced the ALT, AST, ALP and LDH activity (p<0.05), as compared to the DOC treated group.

Table 4 shows a significant increase in liver MDA, caspase-8, NF-κB and IL-1β levels (p<0.05) in DOX (2.0 mg kg^{-1} body weight)- treated rats when compared to the normal control group (p<0.05). The administration of JMAE-SeNPs at the doses of 22.4 and 56 mg kg^{-1} body weight, showed significant decrease in MDA, caspase-8, NF-κB) and IL-1β levels compared to DOX treated group of rats after 4 weeks (p<0.05).

Table 5 shows a significantly (p<0.05) decreased activities of antioxidant parameters of liver (SOD, GPx and GSH) in the DOX-treated rats as compared to the normal control group (p<0.05), indicating acute liver toxicity. Oral administration of 22.4 and 56 mg kg^{-1} body weight of JMAE-SeNPs significantly (p<0.05) enhanced the liver enzymes activities (SOD, GPx and GSH) in rats as compared to the DOX-treated group.

Figure 3 shows the histopathological examination of liver sections of the normal group (I) showing normal hepatic parenchyma; note the normal polyhedral hepatocytes (h), blood sinusoids and central vein (c), (H&E ×400). On the other hand, in the liver of DOX-treated control group (II), showing changes in the portal area; note the congested hepato-portal blood vessel (arrowhead), hyperplastic bile duct (arrow) and leucocytic cells infiltration (*), (H&E X200). Histopathological examination also showed good recovery of DOX-induced liver toxicity when JMAE-SeNPs was administered at 22.4 and 56 mg kg^{-1} body weight as compared to the DOX-treated group and showed almost the same records as Groups III and IV.

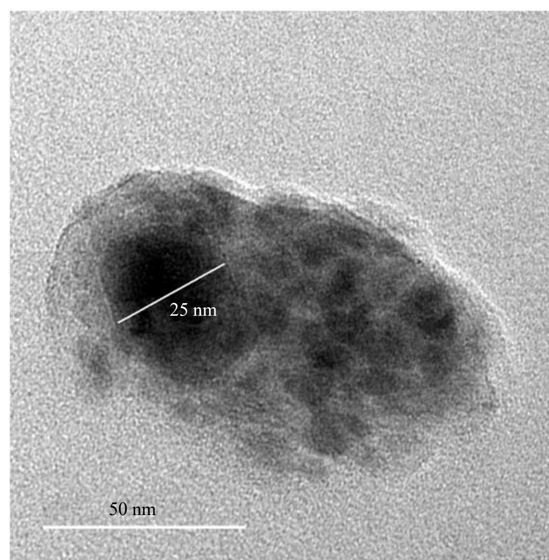

Fig. 1: TEM analysis of SPSNPs

Table 2: Determination of LD_{50} of JMAE-SeNPs given orally in adult rats

Group No.	Dose (mg kg^{-1})	No. of animals/group	No. of dead animals	(Z)	(d)	(Z.d)
1	500	10	0	1.0	250	150
2	750	10	2	2.5	250	650
3	1000	10	3	5.0	250	1250
4	1250	10	7	7.5	250	1875
5	1500	10	8	9.5	250	2375
6	1750	10	10	0	00	6300

$LD_{50} = Dm\left[\frac{\Sigma(Z\times d)}{n}\right]$, $LD_{50} = 1750-\left[\frac{6300}{10}\right] = 1120\ mg\ kg^{-1}$ body weight

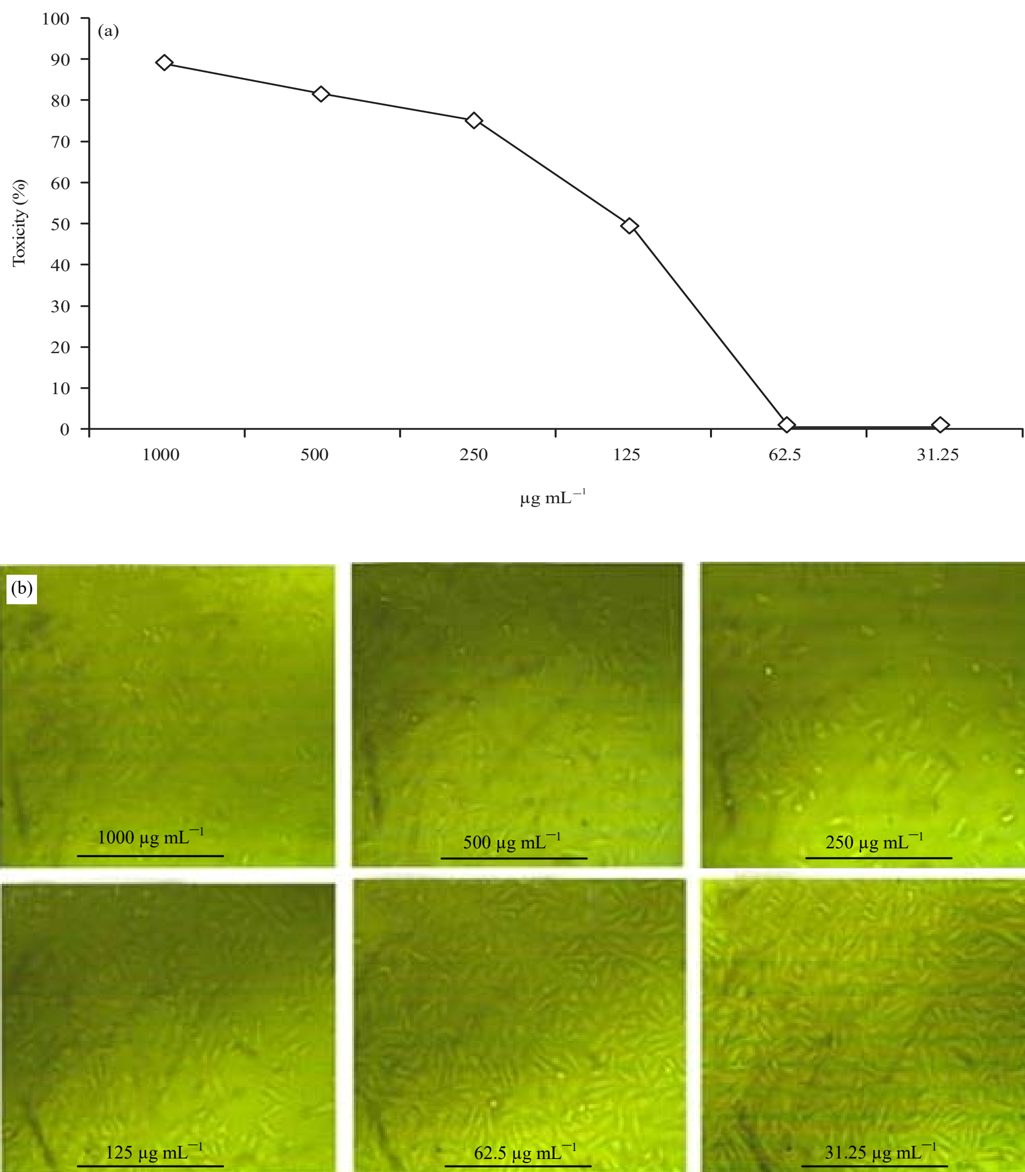

Fig. 2(a-b): IC_{50} and the effect JMAE-SeNPs against Hep-G2 liver carcinoma cell line

Table 3: Effect of JMAE-SeNPs on plasma alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activity in rats treated with DOX

Groups	Treatment description	ALT ($U L^{-1}$)	AST ($U L^{-1}$)	ALP ($U L^{-1}$)	LDH ($U L^{-1}$)
I	Normal control A	21.65 ± 2.10^{a}	17.53 ± 2.85^{a}	74.90 ± 4.37^{a}	143.60 ± 14.33^{a}
II	DOX (2 mg kg^{-1} b.w.)	66.70 ± 4.72^{c}	42.11 ± 3.25^{c}	197.52 ± 8.73^{d}	376.80 ± 21.80^{d}
III	JMAE-SeNPs (22.4 mg kg^{-1} b.w)+DOX (2 mg kg^{-1} b.w.)	29.80 ± 2.43^{b}	22.54 ± 3.11^{b}	104.07 ± 9.64^{c}	172.48 ± 12.87^{c}
IV	JMAE-SeNPs (56 mg kg^{-1} b.w)+DOX (2 mg kg^{-1} b.w.)	22.31 ± 3.50^{a}	19.63 ± 2.76^{a}	85.40 ± 6.55^{b}	151.27 ± 11.40^{b}

Results are presented as Mean±standard deviation of number of observations within each treatment. Data followed by the same letter are not significantly different at $p\leq0.05$, b.w.: Body weight

DISCUSSION

In the present study, DOX (2.0 mg kg^{-1}) was administered one time weekly for 4 weeks. Our results showed that elevation of plasma ALT, AST, ALP and LDH indicated the toxic effect of DOX at this dose and previous studies[41,42] which showed the toxicity of DOX without mortality also confirmed this result. Also, elevation of inflammatory mediators, caspase-8, NF-κB and IL-1β and oxidative stress marker (MDA) proved the DOX toxicity[43].

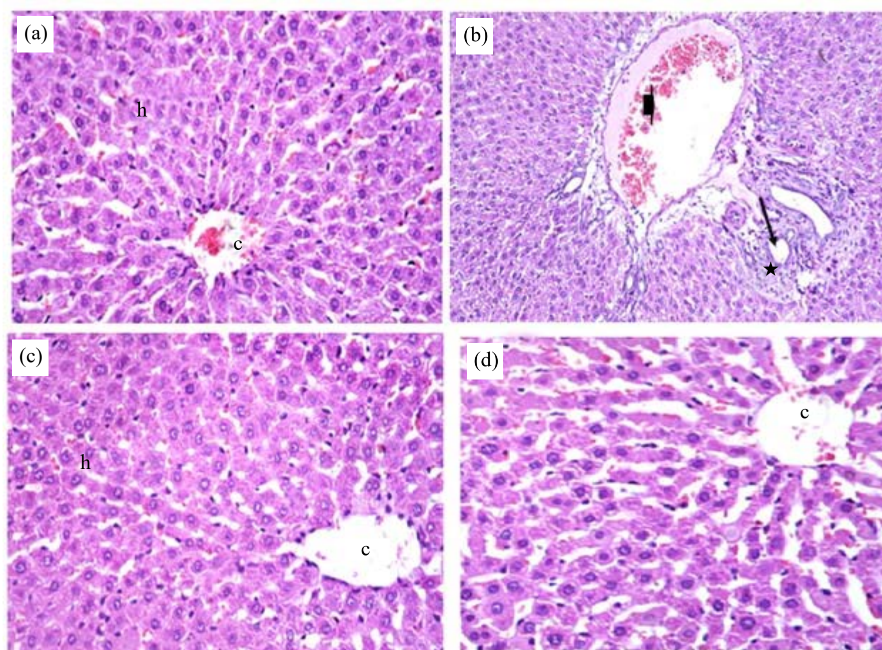

Fig. 3(a-d): Sections stained with hematoxylin and eosin (H&E; 400X) histological examination of rats' liver of different groups compared to control group; (a), Group I: Normal control; (b), Group II: DOX (2.0 mg kg^{-1} body weight) (c); Group III: JMAE-SeNPs was administered at the dose of 22.4 mg kg^{-1} body weight+DOX (2 mg kg^{-1} body weight) (d); Group IV: JMAE-SeNPs was administered at the dose of 56 mg kg^{-1} body weight+DOX (2 mg kg^{-1} body weight)

Note: Normal polyhedral hepatocytes (h), blood sinusoids and central vein (c), (H&E ×400)

Table 4: Effect of JMAE-SeNPs on levels of liver malondialdehyde (MDA), caspase-8, necrosis factor- κB (TNF- κB) and interleukin-1β (IL-1β). in rats treated with DOX

Groups	Treatment description	MDA (nmol mg^{-1} tissue)	Caspase-8 (pg mg^{-1} tissue)	TNF- κB (pg mg^{-1} tissue)	IL-1β (pg mg^{-1} tissue)
I	Normal control A	5.89 ± 0.50^{a}	45.00 ± 4.63^{a}	12.68 ± 1.38^{a}	27.60 ± 3.16^{a}
II	DOX (2 mg kg^{-1} b.w.)	17.33 ± 1.23^{c}	106.33 ± 8.70^{c}	39.80 ± 2.09^{c}	55.40 ± 4.38^{c}
III	JMAE-SeNPs (22.4 mg kg^{-1} b.w)+DOX (2 mg kg^{-1} b.w.)	11.25 ± 1.15^{b}	52.68 ± 3.62^{b}	16.44 ± 1.47^{b}	34.72 ± 2.11^{b}
IV	JMAE-SeNPs (56 mg kg^{-1} b.w) + DOX (2 mg kg^{-1} b.w.)	6.09 ± 0.65^{a}	45.50 ± 2.89^{a}	14.25 ± 1.09^{a}	31.22 ± 3.07^{b}

Results are presented as Mean±standard deviation of number of observations within each treatment. Data followed by the same letter are not significantly different at $p\leq0.05$, b.w.: Body weight

Table 5: Effect of JMAE-SeNPs on levels of liver superoxide dismutase (SOD) and glutathione peroxidase (GPx) and reduced glutathione (GSH) in rats treated with DOX

Groups	Treatment description	SOD	GPx	GSH (mg%)
I	Normal control A	8.90 ± 0.62^{c}	11.63 ± 0.72^{c}	18.76 ± 1.10^{c}
II	DOX (2 mg kg^{-1} b.w.)	3.44 ± 0.21^{a}	5.25 ± 0.43^{a}	6.45 ± 0.42^{a}
III	JMAE-SeNPs (22.4 mg kg^{-1} b.w)+DOX (2 mg kg^{-1} b.w.)	5.04 ± 0.32^{b}	8.77 ± 0.89^{b}	15.98 ± 1.05^{b}
IV	JMAE-SeNPs (56 mg kg^{-1} b.w)+DOX (2 mg kg^{-1} b.w.)	8.10 ± 0.66^{c}	10.64 ± 0.95^{bc}	18.04 ± 1.20^{bc}

Results are presented as Mean±SD for groups of six animals each. Values followed by the same letter are not significantly different at $p\leq0.05$. SOD: one unit of activity was taken as the enzyme reaction, which gave 50% inhibition of NBT reduction in 1 min mg^{-1} protein; GPx: µg of GSH consumed min^{-1} mg protein, b.w.: Body weight

Furthermore, oral administration of JMAE-SeNPs at 22.4 and 56 mg kg^{-1} body weight, provided significant protection against DOX-induced liver toxicity. These effects could be due to the presence of polyphenols of the Jasonia Montana which are beneficial for human health[27,28] and quercetin have been reported to enhance short-term memory performance in animal models[44].

In the present study, elevation of caspase-8, NF-κB and IL-1β and oxidative stress marker (MDA) was observed in DOX-treated rats. Results of the present study are consistent with Pecoraro *et al*.,[45] and Wu *et al*.,[46], who showed the elevation of inflammatory mediator in DOX- treated rats.

The current results showed that JMAE-SeNPs could normalize the levels of caspase-8, NF-κB and IL-1β and MDA in

the DOX-treated group. DOX-induced free radicals regulate cell proliferation and death, as well as gene expression of TNF-β, IL-1β, iNOS and MDA[41,42].

Free radicals, oxidative stress and lipid peroxidation are observed in damaged organ[47]. It has been demonstrated that in chronic liver toxicity, increased liver levels of TNF-β, IL-1β, iNOS and MDA, as well as decreased activity of SOD, GPx and GSH, induce mitochondrial toxicity and free radical generation[48].

The most extensively studied mitogenic and fibrogenic factors are NF-κB, IL-6, iNOS and MDA. JMAE-SeNPs can also inhibit the expression of proinflammatory cytokines[49]. Taken together, these findings suggested that JMAE-SeNPs antifibrotic effect is linked to the inhibition of mitogenic and/or fibrogenic signaling. TNF-κB has been shown to stimulate the formation of NO[50].

JMAE-SeNPs are a powerful reactive oxygen species (ROS) scavenger[46] and normalized the oxidative stress biomarkers (SOD, GPx, GSH and MDA), resulting in decreased oxidative stress, which contributes to DOX's suppression of liver inflammation. In the current study, after DOX administration, there was a significant decrease in liver SOD, GPx and GSH activity.

Endothelial activation was also elicited by TNF-β, IL-1β, iNOS and MDA protein expression, which could be mitigated by Jasonia montana extract[39]. JMAE-SeNPs inhibited H_2O_2-induced monocyte adhesion to HCAECs in a similar concentration range, which is significant. The second significant finding is that resveratrol inhibits TNF-induced NF-B activation in HCAECs[46]. Another study suggested that spirulina extract was effective against iNOS protein expression, TNF-β, IL-1β and MDA -induced NF-B activation in intact blood vessels[39].

According to histological studies, JMAE-SeNPs have a liver-protective effect. Because liver proliferation is an early event in toxicity-related changes, the attenuation of liver injury and fibrosis in rats by JMAE-SeNPs could be associated with a reduction in inflammatory response. To the best of my knowledge, the prophylactic effect of JMAE-SeNPs against DOX-induced liver toxicity has never been reported and this study may be the first of its kind.

CONCLUSION

The current study found that JMAE-SeNPs have potent liver protective activity against DOX-induced liver toxicity by normalizing the levels of oxidative stress biomarkers and inflammatory mediators.

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