RESEARCH ARTICLE Indian Journal of Animal Research, Volume 59 Special Issue: 56-66 (November 2025)

Ameliorative Effects of Dandelion Root Extract (*Taraxacum officinale*) against Silver Nanoparticles-stimulated Hepatotoxicity in Male Albino Rats

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ABSTRACT

Background: Dandelion roots have considerable health benefits including promoting liver health and combating inflammation. Therefore, our study investigated the impacts of dandelion root extract (*Taraxacum officinale*) on AgNPs-triggered hepatotoxicity in rats.

Methods: Herein, 48 adult male albino Wistar rats were randomly distributed into six groups (8 rats/group). As controls, rats from the first group were employed. *T. officinale* (500, 250 mg/kg b.w./day) was administrated orally to the rats of the second and third groups. The AgNPs (1 mg/kg b.w./day) were intraperitoneally injected into the fourth group. Rats of the fifth and sixth groups were treated with (*T. officinale* 500+ AgNPs) and (*T. officinale* 250+ AgNPs). After four weeks, biochemical, histopathological and immunohistochemical evaluations were conducted on the blood samples and liver tissues.

Result: Here, we have manifested that exposure to AgNPs significantly elevated liver enzyme levels alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH), total protein, albumin, Malondialdehyde (MDA) and caspase-3 whereas total bilirubin levels, superoxide dismutase (SOD) and glutathione (GSH), revealed significant decline linked to hepatic damage. Treatment of rats with *T. officinale* showed a pronounced attenuation of the damage caused by AgNPs associated with improvement of biochemical, hepatic histopathological and immunohistochemical alterations. This study shows that sub-chronic oral administration of *T. officinale* in rats protects against AgNPs-stimulated hepatotoxicity. The positive implications may be ascribed to the antioxidant capabilities of *T. officinale*.

Key words: Antioxidants, Dandelion roots (*Taraxacum officinale*), Hepatotoxicity, Oxidative stress, Silver nanoparticles.

INTRODUCTION

Nanoparticles (NPs) are at the forefront of the quickly evolving field of nanotechnology and have attracted significant attention for their use in both the treatment of cancer and as an efficient drug delivery method (Albrahim and Alonazi, 2020). Compared to the original bulk substance, these NPs' average size falls between 1 and 100 nm (Ema *et al.,* 2017). These sizes have distinct chemical and physical characteristics that lead to advanced magnetic, electrical, optical, mechanical and structural qualities (Lekha *et al.,* 2021). Silver NPs (AgNPs) have attracted attention among the many current nanomaterials because of their distinctive physical and biochemical characteristics (Zhang *et al.,* 2016). Also, their exceptional antibacterial activity makes them beneficial for applications in many areas, including biomedicines (Lee and Jun, 2019). However, their concentration in the environment is unknown and they pose a potential threat to the human body organs, including the liver (Xiong *et al.,* 2022). The implications of AgNP accumulation in the liver are inflammation, necrosis and apoptosis (Al-Doaiss *et al.,* 2020).

Oxidative stress is an essential mechanism of AgNP hepatoxicity, reactive oxygen species (ROS) generation and proinflammatory cytokines secretion (Mishra *et al.,* 2016; Blanco *et al.,* 2018; Mao *et al.,* 2018). Salama and her colleagues manifested that oxidative stress, inflammation and ultimately cellular death can be the result of elevated ROS levels, which disrupt intracellular redox balance (Salama *et al.,* 2023). Excessive synthesis of the ROS may lead to heightened lipid peroxidation, damage of mitochondria and apoptosis, beyond the capacity of natural cellular antioxidant defense mechanisms, But the body has a strategy by which it tries to overcome ROS and defend the body through antioxidants the antioxidant defense system and the most important antioxidant enzymes GSH and SOD, which in turn reduce the toxic effects (Flores-López *et al.,* 2019).

Recent years have seen a significant increase in interest in natural product-based medications for preventing and treating liver conditions (Amin *et al.,* 2016; Ayaz *et al.,* 2017; Hamza *et al.,* 2018; Khajuria *et al.,* 2018; Ashktorab *et al.,* 2019). The dandelion *Taraxacum officinale*

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How to cite this article: Aljarari, R.M., Qahl, S.H., Al-Sulami, S.A. and Alzahri, R.Y. (2025). Ameliorative Effects of Dandelion Root Extract (*Taraxacum officinale*) against Silver Nanoparticles-Stimulated Hepatotoxicity in Male Albino Rats. *Indian Journal of Animal Research*. **59 (Special Issue):** 56-66. doi: 10.18805/IJAR.BF-1956.

Submitted: 12-01-2025 **Accepted:** 28-02-2025 **Online:** 15-05-2025

(*T. officinale*) is a perennial herbaceous plant in the Asteraceae family. In many nations, it has been employed as a system for both traditional and contemporary herbal treatment. It has been utilized as a folk remedy for treating chronic liver disorders in many different nations. Moreover, it exhibited numerous health advantages because of its diuretic (Rβcz-Kotilla *et al.,* 1974) and anti-oxidant *in vivo* (Choi *et al.,* 2010) and *In vitro* (Park *et al.,* 2011; Ivanov *et al.,* 2018; Milek *et al.,* 2019), anticancer (Saratale *et al.,* 2018), such as human leukemia, pancreatic, colorectal and prostate cancer cells (Nguyen *et al.,* 2019; Ovadje *et al.,* 2011; Ovadje *et al.,* 2012; Ovadje *et al.,* 2016) and inflammatory (Di Napoli and Zucchetti, 2021). In the Arabian regions, dandelion *T. officinale*, an edible plant, has been utilized as a traditional herbal remedy to cure liver disorders (Schutz *et al.,* 2006). *T. officinale* contains flavonoids and polyphenolic compounds, including sesquiterpene lactones, taraxerol and chlorogenic and chicoric acids, as well as vitamins A, B, C, D, E, lecithin, inositol and minerals like sodium, iron, magnesium, copper, zinc, calcium, phosphorus, silicon and manganese (Pereira *et al.,* 2016; Qadir *et al.,* 2022). It has been shown that the root extract of *T. officinale* may offer protection against certain toxic liver injuries (Cai *et al.,* 2017).

Therefore, we aimed to ascertain the ameliorative impact of *T. Officinale* against AgNPs-triggered hepatotoxicity and explore the underlying mechanisms.

MATERIALS AND METHODS

Dandelion *(T. officinale*) root extract was supplied as herbal supplement capsules (800 mg/capsule) and purchased from (Herbal Factors Company, Coquitlam, Canada). Each capsule was suspended in 10 ml of distilled water shortly before administration (Park *et al.,* 2010). Phosphate buffered saline (PBS) was obtained from the pharmaceutical Solutions Industry, Jeddah, Saudi Arabia). Diethyl ether was obtained from Sigma-Aldrich (GMBH, Munich, Germany). Formaldehyde was purchased from (Riedel-Detain, Sleaze, Germany). The ALT, AST, ALP, LDH, albumin, GSH, SOD, MDA, total bilirubin and protein, were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA) kits (My BioSource, San Diego, U.S.A).

In brief, a cold bath maintained at 6°C to 10°C was used to combine 185 mL of type 1 water (Milli Q) with 5 mL of both 0.05 M sodium citrate (TSC, Sigma Aldrich CAS 6132-04-3) and silver nitrate (AgNO3, PANREAC CAS 7761-88-8). The mixture was centrifugated at 3000 RPM for a duration of 3 minutes. Afterward, 5 mL of 0.05 M sodium borohydride (NaBH4, Sigma-Aldrich CAS 16940-66-2) was progressively introduced. Typically, 1.25 M sodium hydroxide (NaOH, PANREAC CAS 1310-73-2) was employed to adjust the pH to 10. The resulting nanoparticles (NPs) were stored in amber bottles at 4°C and were utilized as mentioned in a previous study (Quintero-Quiroz *et al.,* 2019).

The samples' size and morphology were verified with transmission electron microscopy (TEM) utilizing a Tecnai F20 Super Twin Turbo-molecular Pump (TMP) and a Tecnai G2 200KV TEM (FEI). The samples were generated by depositing a drop of each suspension, about 60 nm thick, onto a carbon membrane (Monteiro *et al.,* 2011) (Fig 1). The sample was examined employing an X-ray diffractometer (XRD) using CuKα radiation, scanning a 2θ range from 10° to 80° (Zhang *et al.,* 2016) (Fig 2).

Here, male albino Wistar strain rats (*Rattus norvegicus*), with a weight range of 140-180 g were employed. The rats were acquired from the experimental animal facility of the Faculty of Pharmacy at King Abdulaziz University, Jeddah, Saudi Arabia. All methods received approval from the Animal Care and Use Committee at King Abdul-Aziz University, Faculty of Pharmacy, Jeddah, Saudi Arabia (Approval number: PH-1444-16). Rats were acclimatized for 7 days before the beginning of the experiment. Standard plastic (polypropylene) cages were used to house the rats, which were maintained in controlled laboratory conditions with a humidity of 65%, a temperature of 20 ± 1°C and a 12:12 h light / dark cycle. Throughout the acclimation phase, the rats were fed daily with normal commercial chow ad libitum and given unrestricted access to water.

Typically, 48 rats were allocated into six experimental groups (n = 8) and were treated as follows:

- Group 1: (Negative control) received an oral administration of saline solution (0.9% NaCl) for four weeksdaily.
- Group 2: Received *T. officinale* root aquatic extract (500 mg/kg b.w.) orally daily for four weeks.
- Group 3: Received *T. officinale* root aquatic extract (250 mg/kg b.w.) orally daily for four weeks.
- Group 4: (positive control), was given AgNPs (1mg/kg b.w.) by intraperitoneal injection (I/P), daily for four weeks.
- Group 5: Received *T. officinale* root aquatic extract (500 mg/kg b.w.) and AgNPs (1 mg/kg b.w.); with one-hour intervals between the two administrations; daily for four weeks.
- Group 6: Received *T. officinale* root aquatic extract (250 mg/kg b.w.) and AgNPs (1 mg/kg b.w.) fo.); with one-hour intervals between the two administrations; daily for four weeks.

The selected dose of AgNPs was selected based on previous research articles (Aboelwafa *et al.,* 2022; Assar *et al.,* 2022; Yousef *et al.,* 2022). Also, the two doses of *T. officinale* root aquatic extract were selected according to Domitrović *et al.* (2010); Fallah *et al*. (2010); Şenocak and Yıldırım (2017); Shaaban *et al*. (2023) for the low dose (250 mg/kg) and according to Fallah *et al*. (2010); Aremu *et al*. (2019); Hamza *et al*. (2020) for the high dose (500 mg/kg).

After the end of the experiment (at 38th day), rats were weighed and anaesthetized utilizing diethyl ether. Blood samples were obtained from the retro-orbital venous plexuses. The serum underwent centrifugation at 2500 rpm for 15 min and was thereafter stored for biochemical analysis at -80°C. The abdomen was dissected and then the liver was isolated, weighed and dissected into two parts. The first section was produced and fixed in 10%

formalin for histopathological and immunohistochemical analysis. A separate portion was homogenized in 4 volumes of phosphate buffer (pH 7.4) for biochemical examination. The liver-to-body weight index was determined by calculating the ratio of liver weight to the rat's final body weight after weighing both the body and liver. The ALT. AST, ALP, LDH, albumin, total bilirubin and protein levels in serum were ascertained by commercial kits, per protocols.

For biochemical evaluation of GSH, SOD and MDA, a part of liver homogenate was centrifuged at 12000 g at 4°C for 20 min. Afterwards, the supernatant was separated and stored at -80°C and the activities of oxidative stress markers were investigated by commercial kits, following the protocols.

Liver tissues fixed in formalin were embedded in paraffin blocks, sliced into 5-micrometer thickness, placed on glass slides and stained with hematoxylin and eosin (HandE) (Bancroft and Gamble, 2008). The prepared liver slices were examined using an Intellisite Ultra-Fast Scanner (Digital Pathology Slide Scanner, Philips FMT0225).

Furthermore, 5-µm formalin-fixed, paraffin-embedded slices were examined with immunohistochemical staining *via* the streptavidin-biotin technique utilizing caspase 3 antibodies as an indicator for programmed cell death (apoptosis), following the aforementioned protocol (Ghonimi *et al.,* 2022).

The statistical analysis was performed with the Statistical Package for Social Science (SPSS program for Windows, version 25). Data were expressed as mean +/- standard error. The difference between different experimental groups was assessed with One Way ANOVA (Tukey test). P-value <0.05 is deemed statistically significant.

RESULTS AND DISCUSSION

Body weight

The initial body weight of different groups ranged from (140 gm to 181 gm). The smallest weight was in the *T. officinale* 250 group (140 gm) in comparison to the control rats (178 gm). However, AgNPs intoxicated rats, (*T. officinale* 500 + AgNPs) and (*T. officinale* 250 + AgNPs) treated rats

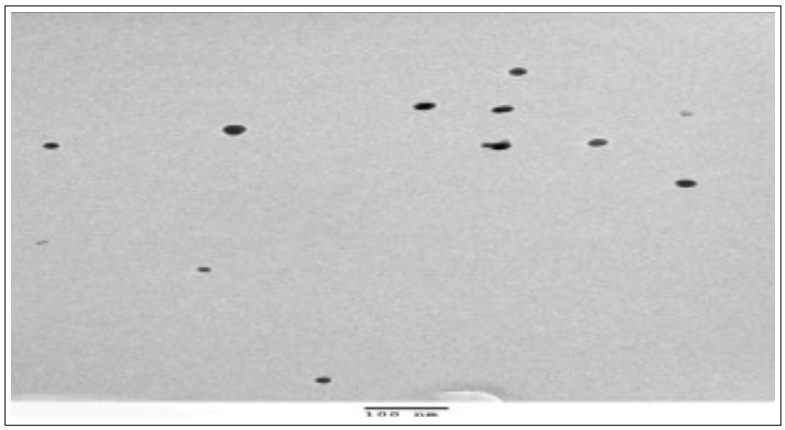


Fig 1: Transmission electron microscope (TEM) micrograph showed silver nanoparticles (AgNPs) with spherical shapes and monodispersed behaviour (Scale 100 nm).

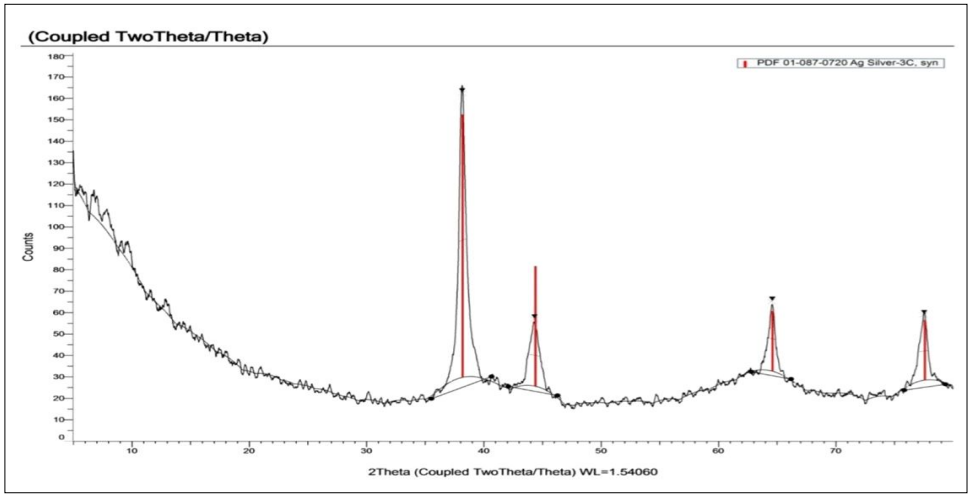


Fig 2: Show the x-ray diffraction pattern of AgNPs with an average crystal particle size of 12 nm.

showed a substantial increment in their initial body weight compared to control. Moreover, no significant difference in ultimate body weight among the various groups was observed. However, the AgNPs intoxicated rats displayed a marked reduction in their body weight compared to other treated groups (Fig 3).

Liver weight index

As depicted in Fig 4 revealed a non-significant difference between different treated groups. However, the liver weight index of AgNP-intoxicated rats declined compared to the control group. Also, (*T. officinale* 500 + AgNPs) treated rats exhibited a reduction in the liver weight index. However, it was not significant.

Liver function analyses

The outcomes manifested that the (ALT, AST, ALP, LDH, albumin and total protein) levels were significantly raised in the serum of the AgNPs group, unlike the control rats ($P<0.05$). Treatment with (*T. officinale* 500+ AgNPs) and (*T. officinale* 250+ AgNPs) significantly mitigated (ALT, AST, ALP, LDH, albumin and total protein) levels contrasted with AgNPs group ($P<0.05$). The total bilirubin level in serum revealed a significant decline in the AgNPs group, unlike the control rats ($P< 0.05$). Nevertheless, treatment with (*T. officinale* 500+ AgNPs and *T. officinale* 250+ AgNPs) caused significant increases in total bilirubin compared with the AgNPs group ($P<0.05$; Table 1).

Liver oxidative stress markers

Here, we found that the AgNPs group experienced a significant decline in the GSH and SOD levels compared to the control rats ($P<0.05$). Treatment with (*T. officinale* 500+ AgNPs) and (*T. officinale* 250+ AgNPs) caused significant increases in GSH and SOD levels compared with the AgNPs group ($P<0.05$). The AgNPs group exhibited significantly elevated MDA levels in comparison with control rats ($P<0.05$). Nevertheless, treatment of rats with (*T. officinale* 500+ AgNPs) and (*T. officinale* 250+ AgNPs) caused significant decreases in MDA levels compared with the AgNPs group ($P <0.05$, Fig 5a-c).

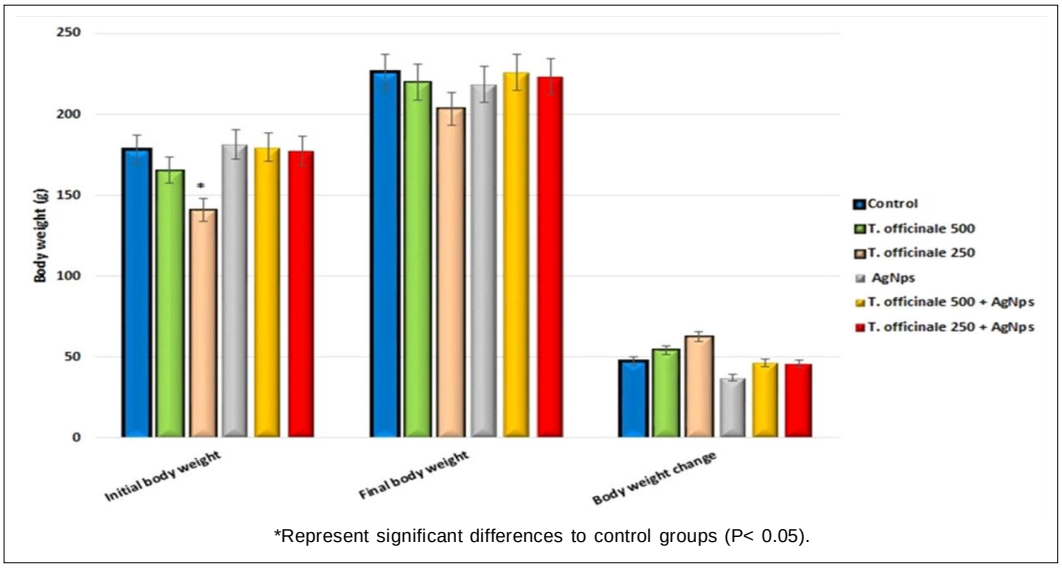


Fig 3: Changes in body weight (g) after four weeks of different experimental groups. Data are mean±SE of eight animals in each group.

Table 1: Levels of serum ALT, AST, ALP, LDH, Albumin, Total bilirubin and Total protein of different experimental groups.

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	Albumin (g/dl)	Total bilirubin (mg/dl)	Total protein (g/dl)
Control	18.30±1.56	25.57±2.06	47±2.31	150.33±8.51	6.53±0.23	4.51±0.45	0.37±0.04
T. officinale 500	18.57±2.23	22.17±1.71	52.67±6.77	163.33±8.82	6.00±0.26	4.11±0.31	0.40±0.09
T. officinale 250	12.37±0.47	14.73±0.94	47.33±1.45	145.67±2.96	5.87±0.26	5.7±0.76	0.81±0.19
AgNPs	99.67±12.78*	114.90±13.62*	147.33±8.09*	492±28.18*	9.83±0.26*	1.73±0.23*	1.40±0.09*
T. officinale 500 + AgNps	14.40 ±1.91#	17.57±2.06#	52.67±6.17#	150±12.06#	5.9±0.26#	4.57±0.38#	0.61±0.13#
T. officinale 250 + AgNps	16.40±2.51#	20.47±2.42#	59.33±9.39#	168.67±10.84#	6.17±0.41#	5.13±0.47#	0.52±0.16#

*Indicates a significant difference versus control. # Indicates a significant difference versus AgNPs.

Liver histopathological examination

Histopathological examination of liver sections is illustrated (Fig 6a-f). Histological studies revealed that the control group showed normal hepatic architecture (Fig 6a). The liver structure of the group treated with (*T. officinale* 500 mg) showed that the liver histology exhibited a structure comparable to that of the control group, except for minor histological alterations (Fig 6b). The structure of the liver treated with (*T. officinale* 250 mg) exhibited a resemblance to the control group, characterized by relatively normal hepatocytes with rounded vesicular nuclei and eosinophilic cytoplasm containing basophilic granules (Fig 6c). The alterations in the liver of the AgNPs group demonstrated severe damage in the liver which was revealed as inflammatory, degenerative, necrotic and hyperplastic alterations. The AgNPs-intoxicated group showed obvious histopathological changes; these include degenerations of hepatocytes leaving empty spaces, dilated hyperemic and congested blood sinusoids, degenerated hepatocytes and some of them appeared with eosinophilic cytoplasm and deeply stained pyknotic nuclei. The portal tract demonstrated congested and dilated portal vein, mononuclear cell infiltrations and necrotic empty spaces left by degenerated hepatocytes (Fig 6d). In rats treated

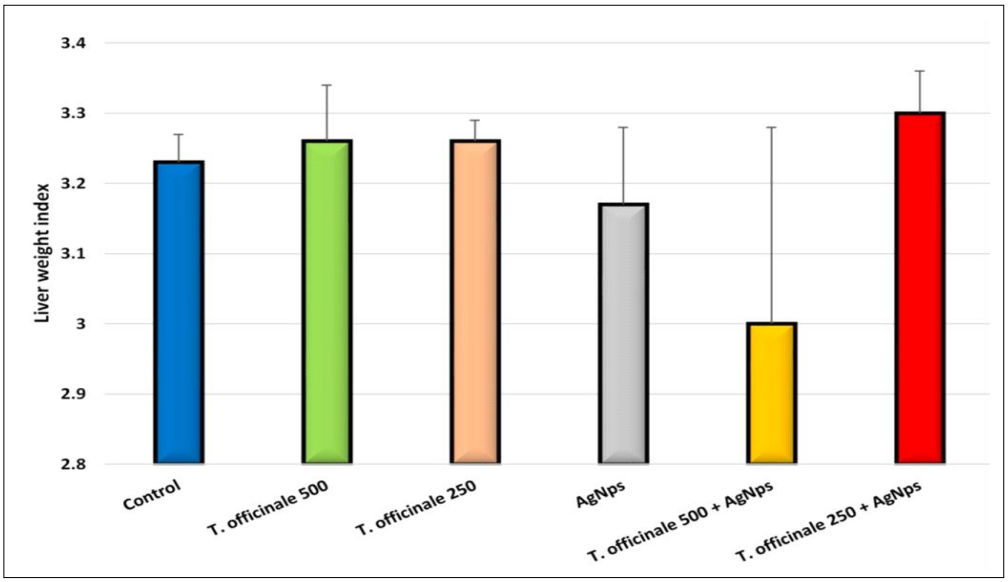


Fig 4: Liver weight index (%) of different experimental groups. Data are mean±SE of eight animals in each group.

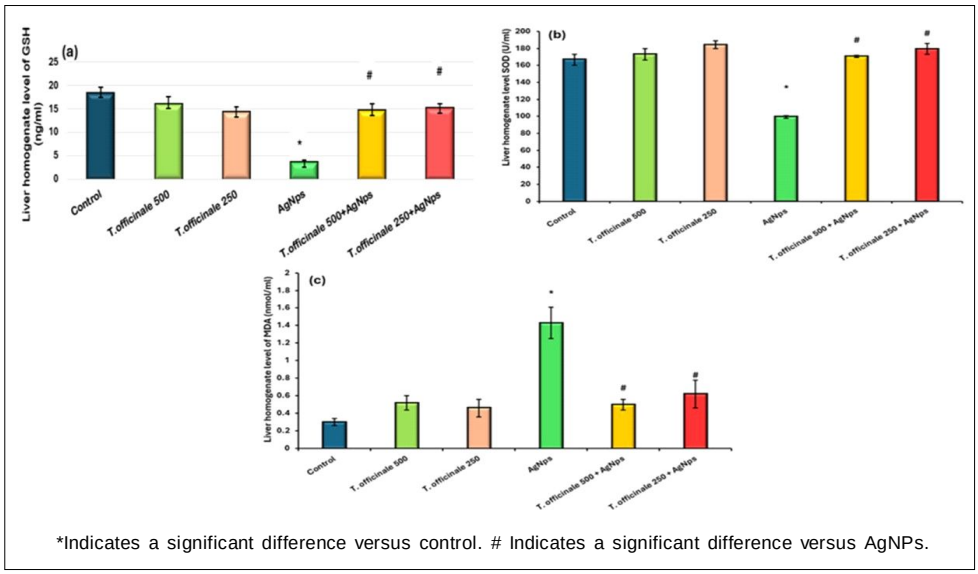


Fig 5(a-c): Levels of liver homogenate (a) GSH, (b) SOD, (c) MDA of different experimental groups.

with (*T. officinale* 500+AgNPs) and (*T. officinale* 250+AgNPs) the hepatic cellularity had significantly improved, according to light microscopic studies.

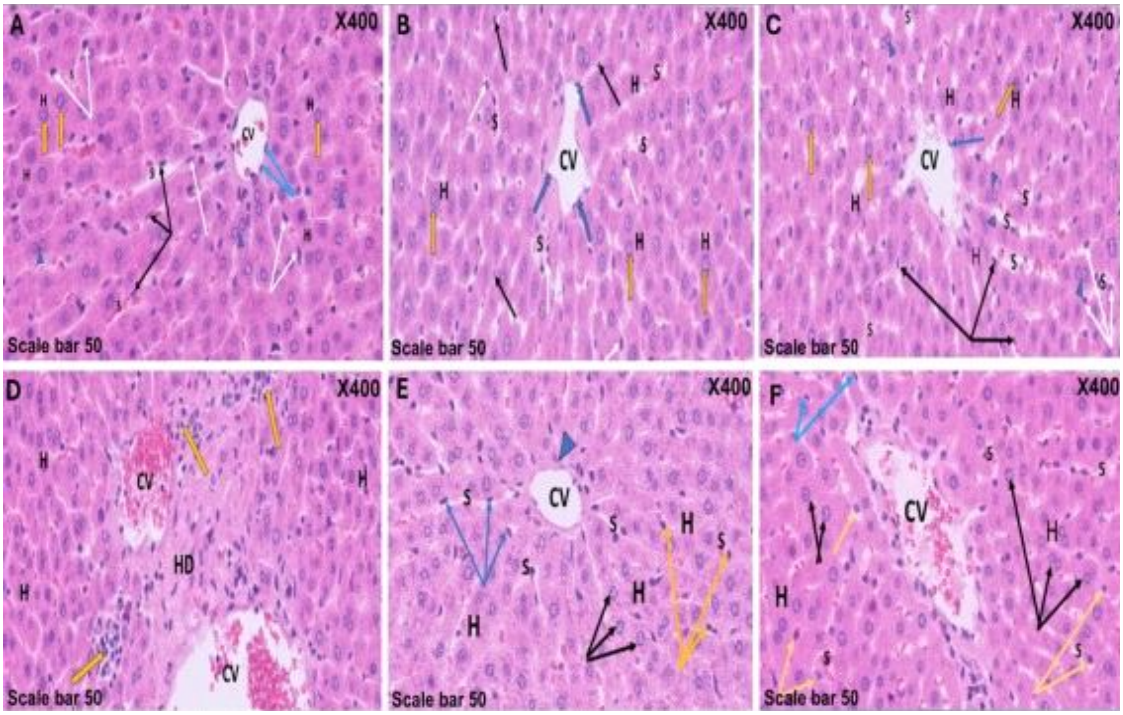
Immunohistochemical examination of Caspase-3

Immunostaining of caspase-3 in the liver manifested adverse caspase-3 expression in the control, *(T. officinale* 500) and (*T. officinale* 250) groups (Fig 7a-c). Conversely, the AgNPs group revealed positive caspase-3 expression in hepatic cells (Fig 7d). Moreover, mitigated caspase-3 expression was manifested in the liver of *(T. officinale* 500+AgNPs) group (Fig 7e). Also, moderate caspase-3 expression was revealed in the liver of rats treated with (*T. officinale* 250+AgNPs; Fig 7f).

The unique physicochemical features of AgNPs make them potentially useful in cosmetics, biosensing, imaging, home products, medicine and research laboratories (Assar *et al.,* 2022). The increasing usage of AgNPs in the last decade has resulted in several issues related to the environment and human health (Syafiuddin *et al.,* 2017). Therefore, a greater understanding of AgNP toxicity and its underlying mechanisms is a must. Natural product-derived drugs have garnered significant interest in preventing and treating liver conditions (Li *et al.,* 2018). *T. officinale* was considered one of the beneficial plants in maintaining liver homeostasis (Ignat *et al.,* 2021).

Here, we aimed to ascertain the hepatoprotective implications of *T. officinale* versus AgNPs-triggered toxicity in adult male albino rats. Rats exposed to AgNPs showed significant body loss, liver function reduction, antioxidant defence system disruption and histopathological alterations of the liver architecture associated with extensive immunoreactivity against the anti-caspase-3 antibody.

Body weight change is a marker of a drug or any agent's substantial toxicity (Zainal *et al.,* 2020). Herein, our findings demonstrated that the body weight was decreased in rats intoxicated with AgNPs contrasted with the control group. Similar studies manifested that exposure to AgNPs can



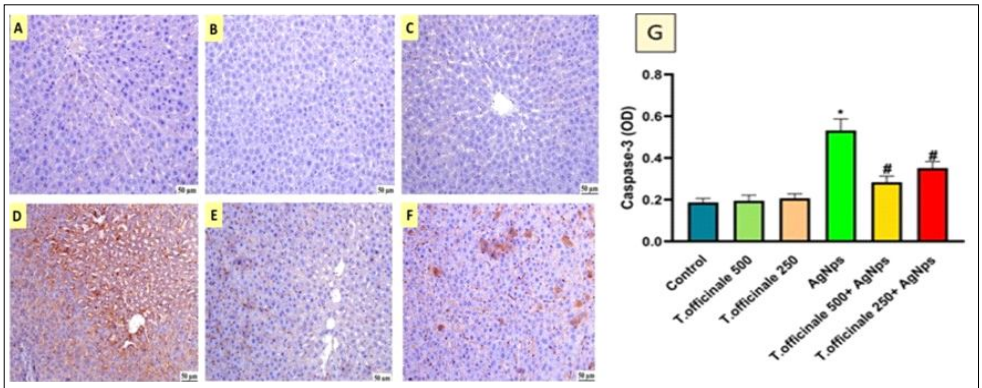
(A) liver tissue section from the control group showing normal hepatocytes (H) with rounded vesicular nuclei (yellow arrows) and normal blood sinusoids (S) lined with endothelial cells (black arrows) and Von Kupffer cells (white arrows). (BandC) liver tissue section from (*T. officinale* 500), (*T. officinale* 250) groups rats showing normal hepatocyte (H) with rounded vesicular nuclei. (D) AgNPs group showing mononuclear leukocytic infiltration (yellow arrows), hydropic degenerations of hepatocytes (HD) around the dilated and congested central vein (CV), eosinophilic hepatocytes (H) with small deeply stained pyknotic nuclei were seen. (E) (*T. officinale* 500+ AgNPs) group showing good improvement in the histological structure of the liver. The normal hepatocytes (H) with eosinophilic cytoplasm and rounded vesicular nuclei (black arrows) radiating from the central vein (CV). The blood sinusoids (S) appeared normally lined with endothelial cells (blue arrows) and Von Kupffer cells (yellow arrows). (F) (*T. officinale* 250+ AgNPs) group showing improvement in the histological structure of the liver with normal hepatocytes(H) with rounded vesicular nuclei (black arrows) radiating from the central vein (CV) which showed slight dilatation and congestion.

Fig 6 (A-F): Photomicrograph sections in the hepatic tissue of rats (Hand E; X400- scale bar 50).

result in weight loss (El-Naggar *et al.,* 2021; Assar *et al.,* 2022; Olugbodi *et al.,* 2023). Conversely, concomitant administration of different doses of *T. officinale* (500 and 250 mg/kg) with AgNPs results in effective management of weight loss compared to rats in the AgNPs group. This finding was aligned with an earlier study (Tan *et al.,* 2017) that suggested the increased growth performance of juvenile golden pompano *Trachinotus ovatus* after dietary *T. officinale* extracts were administered. Also, (Adelakun *et al*., 2024) reported that treatment of diabetic rats with *T. officinale* extract raised the rats' body weight Concerning liver weight index, the current study showed no significant change in the liver weight index in AgNPs-intoxicated rats compared to the control group. These results agreed with the previous study by Rezaei *et al*. (2018). Also, this outcome was consistent with a previous study by Fahmy *et al.* (2020), which reported that rats administrated different oral doses of AgNPs (5, 25 and 50 mg/kg b.w.) five days a week for three months did not exhibit any appreciable changes in their absolute or relative liver weight. Furthermore, Assar *et al*. (2022) reported that adult rats treated with AgNPs for a period of 15 and 30 days showed a decrease in liver weight. This decrease in liver weight might be attributed to a rise in lipid peroxidation, leading to structural changes in lipid vacuoles. On the other hand, (*T. officinale* 500 mg + AgNPs) treated rats displayed a decrease in the liver weight index compared to the AgNPs group. These results agreed with the previous study by Mahesh *et al*. (2010).

The intracellular enzyme release is a significant marker of hepatocyte injury (Abdelkader *et al.,* 2020). Rats intoxicated with AgNPs exhibited significantly elevated ALT, AST, ALP, LDH, albumin and total protein levels, with a significant decline in total bilirubin levels in comparison with control rats. Similarly, previous research suggested that the toxic effects of AgNPs on rat bodies can affect liver functions. This may be attributed to the AgNPs' free radicals that cause hepatocytes to release ALT and allow it to enter the blood (Abd El-Maksoud *et al.,* 2019; Salama *et al.,* 2023). Rats responded to external stimuli by phagocytosing AgNPs with a rise in the number of WBCs (Behzadi *et al.,* 2017). However, treatment with various dosages of *T. officinale* (500 and 250 mg/kg) showed a marked reduction in the liver function enzymes associated with marked elevation of the serum total bilirubin. A previous study demonstrated that *T. officinale* improved the liver function of rats subjected to CCL4 (Hamza *et al.,* 2020). Also, Devaraj discussed the hepatoprotective properties of dandelion (*T. officinale*), especially against various chronic liver diseases (Devaraj, 2016).

Furthermore, in this study, exposure of rats to AgNPs disrupts the antioxidant redox system, including GSH and SOD which aligned with prior research (Ansar *et al.,* 2017). The AgNPs intoxicated rats exhibited significantly raised MDA levels. The AgNP toxicity leads to oxidative stress that results in enhancing MDA production in hepatocytes (Fatemi *et al.,* 2017). These findings corroborate prior research (Moradi- Sardareh *et al.,* 2018; El-Naggar *et al.,* 2021). However, treatment with various doses of *T. officinale* (500 and 250 mg/kg) results in significantly reduced MDA levels linked to a marked increment in the GSH and SOD levels. These outcomes were consistent with earlier research that showed that dandelion (*T. officinale*) treatment before monosodium glutamate exposure led to a significant rise in the GSH levels and a significant decline in the MDA levels (Hussein and Jawad, 2023). Also, Hamza and his colleagues demonstrated the ameliorative impact of dandelion (*T. officinale*) on CCL4-triggered liver oxidative stress as it



(A), (B) and (C) Control, (*T. officinale* 500), (*T. officinale* 250) showing negative expression f caspase 3. (D) AgNPs group showing positive expression of caspase 3. (E) (*T. officinale* 500+ gNPs) group showing lower expression of caspase 3. (F) (*T. officinale* 250+AgNPs) group showing moderate lower expression of caspase 3, scale bar 50 µm. (G) Quantitative image analysis for immunohistochemical staining showed a significant increase in caspase-3 expression in the liver of AgNPs-intoxicated group. *(T. officinale* 500 and 250) remarkably ameliorated caspase-3 expression in the liver tissues of rats exposed to AgNPs respectively. Results are shown as mean ± SE. *p < 0.05 versus control group; #p < 0.05 versus AgNPs group.

Fig 7 (A-F): Photomicrographs of the immunohistochemical stain of the liver against anti-caspase-3 antibody.

showed the best efficacy in normalizing the hepatic content of MDA and SOD activities (Hamza *et al.,* 2020).

All of these outcomes were verified by the histopathological investigation of the liver. The AgNPs-intoxicated group showed obvious histopathological changes; these include degenerations of hepatocytes leaving empty spaces, dilated hyperemic and congested blood sinusoids, degenerated hepatocytes and some of them appeared with eosinophilic cytoplasm and deeply stained pyknotic nuclei. The portal tract revealed congested and dilated portal veins, mononuclear cell infiltrations and necrotic empty spaces left by degenerated hepatocytes. Our outcomes are in accordance with prior research that demonstrated that exposure to AgNPs for 28 days led to congestion of central venules, abnormal morphology of hepatocytes and the blood sinusoids that appear infiltrated by inflammatory cells (Olugbodi *et al.,* 2023). Also, Hamza and his colleagues reported that AgNPs induced degenerative alterations in the liver, kidney and cardiac tissue of male rats (Hamza *et al.,* 2020). Treatment with (*T. officinale* 500 mg and 250 mg) demonstrated a liver structure comparable to that of the control group, with very minor histological alterations. Furthermore, the livers of rats administered (*T. officinale* 500 mg + AgNPs) exhibited significant protection of hepatic cells against necrotic cell death, in contrast to the extensive liver damage found in the AgNPs-treated group. Most of the hepatocytes appeared normal in histological structures. Administration of (*T. officinale* 250 mg+ AgNPs) showed alleviated inflammation, edema, leucocytic cell infiltration, necrotizing hepatocytes and connective tissue fibre propagation which is produced by AgNP intoxication. The histological architecture of the liver of rats treated with (*T. officinale* 500 mg+ AgNPs) group appeared more likely similar to the control group compared to that of (*T. officinale* 250 mg+ AgNPs) group. Our findings agree with the findings of earlier research observed that the hepatic injuries were significantly reduced by *T. officinale* root extract pretreatments (Pfingstgraf *et al.,* 2021). Microscopic examination of the hepatic tissue of rats co-treated with *T. officinale* demonstrated an enhancement in liver histoarchitecture, like that of the control rat. The impacts of *T. officinale* roots can be attributed to their high inulin content (Jalili *et al.,* 2020). Here, we demonstrated that the hepatoprotective abilities of *T. officinale* are more effective in inhibiting liver fibrosis and inflammation. This could be due to the variations in classes and contents of polyphenolic compounds. The roots of *T. officinale* include several phytochemicals, encompassing sesquiterpene lactones, polysaccharides, terpenoids and phenolic compounds having antioxidant properties (Qadir *et al.,* 2022; Ürüşan, 2023).

Regarding the immunohistochemistry reactivity of liver tissue to the anti-caspase-3 antibody, the AgNPs intoxicated group displayed severe immunoreactivity confirming widespread apoptosis. These outcomes aligned with previous studies (Shehata *et al.,* 2022; Yousef *et al.,* 2022). Conversely, administration of *T. officinale* at various doses (500 and 250 mg/kg) has protective effects against apoptosis as confirmed in a previous study (Abdel-magied *et al.,* 2019).

CONCLUSION

This study demonstrated that *T. officinal* roots can effectively protect against AgNP-triggered hepatotoxicity in male rats through their antioxidant potential activity.

Informed consent

The experimental design was approved by the Animal Care and Use Committee at King Abdul-Aziz University, Faculty of Pharmacy, Jeddah, Saudi Arabia (Approval number: PH-1444-16).

Conflict of interest

The authors declare no conflict of interest.

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