

Biochemical Modulatory and Protective Effects of the Hydroalcoholic Extract of *Scrophularia striata* on the Hepatotoxicity of Silver Nanoparticles in the Rat Model

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Abstract

BACKGROUND: Silver nanoparticles (AgNPs) are widely used in various products. On the other hand, they can cause a variety of toxicity in living organisms, such as biochemical changes and oxidative stress in the liver. *Scrophularia striata* plant can affect the toxicity of AgNPs in diverse parts of the body due to the potent antioxidant compounds.

OBJECTIVES: The present study aimed to investigate the modulatory impact of the hydroalcoholic extract of *Scrophularia striata* on the hepatotoxicity and oxidative stress caused by AgNPs in male Wistar rats. The measured hepatic enzymes and serum biochemical metabolites included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transferase, albumin, Globulin, total protein, blood urea nitrogen, creatinine, total bilirubin, and direct bilirubin. In addition, the assessed blood oxidative stress markers entailed malondialdehyde, total antioxidant capacity, catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx).

METHODS: A total of 30 male rats with an average weight of 200±20 g were randomly assigned to five experimental groups of six. Animals in group 1 as the negative control received 2 ml distilled water and in group 2 as positive control received 200 ppm AgNPs (i.e., hepatotoxic dose). The rats in groups 3, 4, and 5 received 20, 60, and 180 mg/kg *Scrophularia striata* extract and 200 ppm AgNPs in 30 days, respectively. The animals were sacrificed under slight anesthesia 24 h after the last treatment.

RESULTS: Hepatic enzymes, serum biochemical metabolites, and oxidative stress markers, mainly CAT, SOD, and GPx in groups 4 and 5 were significantly different from the positive and negative control groups ($P<0.05$).

CONCLUSIONS: *Scrophularia striata* plant owing to the presence of some special ingredients, such as flavonoids can compensate for the side effects of AgNPs in the body.

KEYWORDS: Hepatic enzymes, Hepatotoxicity, Oxidative stress, *Scrophularia striata*, Silver nanoparticle

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Introduction

Metal nanoparticles (NPs) have attracted much attention due to their extensive use in biomedicine and industry (Bindhu *et al.*, 2015; Abdelmoneim *et al.*, 2016; Agrawal *et al.*, 2018). Several highly necessary properties have been noted for NPs that make them useful for specific applications. At the same time, they may also be associated with undesirable biological/toxicological reactivity (Oberdörster *et al.*, 2010; Adeyemi *et al.*, 2015). Studies have shown that NPs can pass through cell membranes and interact with biomolecules causing damage to DNA and proteins, as well as altering the cell (Ahamed *et al.*, 2008; Iversen *et al.*, 2009; Maneewattanapinyo *et al.*, 2011). Moreover, these particles might result in neurotoxicity due to crossing the blood-brain barrier (Rahman *et al.*, 2009; Gonzalez *et al.*, 2017). Therefore, there are growing concerns about the safety of NPs for human health and the environment that necessitate further research on the safety of metal NPs (Adeyemi *et al.*, 2014). Studies on some metal-based NPs (e.g. Ag, Au, and Cu) demonstrated their toxic properties at some doses (Pan *et al.*, 2007). Among the nanomaterials, silver NPs (AgNPs), as a product of nanotechnology, has gained interest because of their distinctive properties, such as good conductivity, chemical stability, and catalytic effect along with antibacterial, antifungal, antiviral, and anti-inflammatory activities (Ivask *et al.*, 2014; Franci *et al.*, 2015). The toxicity of AgNPs was reported to be dependent on various factors, including particle size, shape, and capping agent (León-Silva *et al.*, 2016). Toxicity induced by AgNPs and the role of oxidative stress in this process were demonstrated in human cells (Kim and Choi, 2009; Adeyemi and Orekoya, 2014). On the other hand, medicinal plants and natural products have been used for centuries as traditional treatments for numerous diseases (Cock *et al.*, 2015). Most pharmacological activities of medicinal plants are primarily attributed to their phytochemical constituents (Gautam and Kumar, 2012; Chung *et al.*, 2016). In the western provinces of Iran, the snapdragon plant with the scientific name *Scrophularia striata* Boiss has traditional medical usage. Different extracts of this plant are traditionally used in treating infectious diseases. The pharmaceutical activities and positive effects of

Scrophularia striata extract, including wound healing (Ghashghaii *et al.*, 2017; Haddadi *et al.*, 2019), antibacterial effects (Zamanian *et al.*, 2013), anti-inflammatory activities (Mahboubi *et al.*, 2013), analgesic impact (Nasri *et al.*, 2013), anti-cancer properties (Rezaie *et al.*, 2010), antioxidant capacity (Javan *et al.*, 2015), reducing edema, T-cells proliferation, and nitric oxide production inhibition have been studied (Azadmehr *et al.*, 2009). A review of the literature revealed that no study has been performed on the protective effects of *Scrophularia striata* against the toxicity of AgNPs. Consequently, the present study was conducted to determine the biochemical modulatory and protective impacts of the hydroalcoholic extract of *Scrophularia striata* on the hepatotoxicity of AgNPs in the rat model.

Materials and Methods

Plant Sample Collection

The medicinal plant *Scrophularia striata* was collected from mountains around Kermanshah province, Iran in the spring. A botanist confirmed the plant specification with the code *NO: 42801, Kuh.*

Preparation of Hydroalcoholic Extract

First, the plant was cleaned and dried at a temperature of 25°C without exposure to direct sunshine (in the shade). An amount of 250 g of the powdered leaf was extracted with 750 mL ethanol in a cold maceration process for 48 h. The crude aqueous extract was concentrated using a rotary evaporator. The evaporator was kept at a temperature of 40°C. The mixture was allowed to settle before the concentration process followed by elutriating and filtering the supernatant with a Cartouche paper. The dry extract was obtained at a value of 0.22 mg (Nikbakht-Brujeni *et al.*, 2013).

Preparation of Nanoparticles

The AgNPs solution with a concentration of 4000 PPM was prepared from the Pishgaman Iranian Nanomaterial Company (Iran). The AgNPs were 5-8 nm in diameter and were filtered using a 0.22 µM filter by UV-Visible spectrophotometry (Biotek Epoch, USA), and inductively coupled plasma optical emission spectrometry (ICP-OES, Cambridge, United Kingdom). Moreover, the physical and

chemical properties were confirmed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (Figure 1). Standardization was performed by Pishgaman Iran Nanomaterials Company. Briefly, the preparation and characterization of AgNPs were carried out by adding 100 mM silver nitrate to 1% (w/v) tannic acid solution (pH adjusted at 8 by adding 150 mM potassium carbonate) of polyvinyl pyrrolidone (PVP). The AgNP solution became pale yellow. To obtain the toxic concentration of 200 ppm, the original solution was diluted to 20 units, following the manufacturer's instructions. Finally, animals were gavaged daily for 30 days. The hepatotoxicity of NPs at a dose of 200 ppm was determined based on similar studies (Shariatzadeh *et al.*, 2016; Prakash *et al.*, 2017).

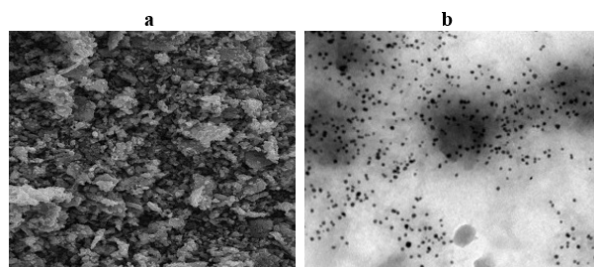


Figure 1. a) SEM and b) TEM images of AgNPs

Experimental Animals

Animals and Treatments

The study design was approved by the Research Deputy of Razi University, Kermanshah, Iran with the ethical code of *NO*: 396.2.038 on 30.1.2018. The handling of animals was and consistent with relevant guidelines as approved by the Institutional Ethics Committee. A total of 30 male Wistar rats weighing 200 ± 20 g were acclimatized for two weeks. The animals were housed in standard plastic cages at a temperature of $25 \pm 3^\circ\text{C}$ under standard environmental and nutritional conditions of the light and dark cycles of 12 h with free access to standard food and clean water.

Study Groups

Group 1 (NC: negative control): received 2 mL of distilled water

Group 2 (PC: positive control): received 200 ppm AgNPs

Group 3 (A): received 20 mg/kg of *Scrophularia striata* extract and 200 ppm AgNPs

Group 4 (B): received 60 mg/kg of *Scrophularia striata* extract and 200 ppm AgNPs

Group 5 (C): received 180 mg/kg of *Scrophularia striata* extract and 200 ppm AgNPs

The animals were given oral daily treatments for 30 days. The election of doses used is premised on previous reports (Naqvi *et al.*, 2010; Agarwal *et al.*, 2013).

Animals Euthanasia

At the end of treatment (30 days), animals were euthanized by the intraperitoneal injection of 1 mg/kg xylazine HCl (xylazine 2%, Alfasan, Netherlands) and 0.5 mg/kg ketamine HCl (ketamine 5%, Trittau, Germany).

Serum Biochemical Analysis

Blood samples were collected into standard laboratory Eppendorf tubes. The collected blood specimens were centrifuged at 12000 g for 10 min (Hettich, United Kingdom), and the sera were kept at 4°C until measurements. The parameters were assessed using an automated biochemical analyzer (SK3002-4040, Sinothinker, China).

Hepatic Enzymes and Serum Biochemical Metabolites

Hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured by commercial kits (Randox, United Kingdom). In addition, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), albumin (ALB), globulin, total protein (TP), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin (TBIL), and direct bilirubin (DBIL) were assessed using commercial kits (Pars Azmoon Co., Iran) and UV/V spectrophotometer (Shimadzu, Kyoto, Japan) in rats serum samples (Azadmehr *et al.*, 2009).

Oxidative Stress Assays

Malondialdehyde (MDA) based on reaction by optical absorption spectrophotometry (Shimadzu, Kyoto, Japan), total antioxidant capacity (TAC) according to the ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] radical reduction, and cation antioxidant molecules by using Randox kits (UK, Randox), catalase (CAT) by using Enzyme Activity kit (NactazTM-Catalase), superoxide dismutase

Table 1. The biochemical modulatory effects of *Scrophularia Striata* extract on Hepatic Enzymes & serum metabolites caused by the hepatotoxicity of AgNPs 200 PPM

Parameters	NC *	PC #	A	B	C
ALT(IU/L)	67.7±1.78	107.75±3.81	80.41±2.75b	76.41±4.53a	81.44±14.72b
AST (IU/L)	87.9±2.65	235.4±4.59	184.31±2.92c	160.71±11.85b	154.17±55.75a
ALP (IU/L)	204.7±3.59	345.2±3.62	302.21±4.6c	270.71±8.73b	273.79±49.22b
LDH (IU/L)	651.16±7.07	947.2±4.2	871.41±2.4c	859.07±20.77b	838.07±101.27a
GGT (IU/L)	5.1±0.37	7.4±0.66	6.8±0.28b	6.4±0.43b	6.36±0.87b
Alb (mg/dL)	3.7±0.29	2.5±0.28	3.1±0.26a	3.21±0.47a	3.48±0.6a
Glo (mg/dL)	3.7±0.52	2.9±0.62	3.1±0.32a	2.7±0.46b	3.3±0.16a
TP (mg/dL)	7.4±0.51	5.4±0.47	5.9±0.34b	6.5±0.57a	6.38±0.8a
BUN (mg/dL)	13±1.05	41.31±2.26	32.3±1.4c	35.2±2.52c	30.48±9.75b
Cr (mg/dL)	0.40±0.03	0.80±0.07	0.76±0.05b	0.72±0.07b	0.68±0.14a
BIL.T (mg/dL)	0.55±0.04	0.76±0.03	0.75±0.08c	0.72±0.02c	0.68±0.02b
BIL.D (mg/dL)	0.11±0.01	0.19±0.02	0.19±0.01b	0.17±0.03a	0.16±0.01a

Notice: The values of the small letters **a**, **b** & **c** indicate a significant difference between the studied groups in comparison with the PC # and got close to the NC* groups respectively ($P<0.05$). NC: Negative control, PC: Positive control, A: 20mg/kg, B: 60mg/kg, C: 180mg/kg

(SOD) and glutathione peroxidase (GPx) based on Formazone optical absorption in comparison with a standard curve were determined (Shariatzadeh *et al.*, 2016).

The present study was approved (Use of laboratory animals) by the research council of Razi University with the code NO: 396.2.038, adopted on 30.1.2018.

Data Analysis

The data were statistically analyzed by one-way analysis of variance and Tukey post-hoc test using the SPSS software version 18 (IBM, Chicago, Ill., USA). All results are shown as mean±SEM and P-value<0.05 is considered significant.

Results

The results of the current study showed that all studied factors (hepatic enzymes and serum metabolites) increased in the positive control group, compared to the negative control group. Furthermore, the administration of *Scrophularia striata* hydroalcoholic extract in treatment groups (20, 60, and 180 mg/kg) along with 200 ppm AgNPs (dose of

hepatotoxicity) caused alterations in serum metabolites in groups 4 (60 mg/kg) and 5 (180 mg/kg), compared to the positive control group ($P<0.05$). Our findings revealed that *Scrophularia striata* hydroalcoholic extract could modulate the cytotoxic effects of AgNPs in rats.

Accordingly, the dosage of the extract at concentrations 20, 60, and 180 mg/kg (groups 3, 4, and 5) caused the levels of ALP, ALT, and AST to get close to the negative control. The order of the intensity of the extract effect on ALT (76.41±4.53 IU/L), AST (154.17±55.75 IU/L), and ALP (270.71±8.73 IU/L) was concentrations 60, 180, and 60 mg/kg (Table 1). The results showed that the levels of LDH and GGT changed, in comparison with the positive and negative controls. The highest dosage of *Scrophularia striata* extract at concentration 180 mg/kg (group 5) led to altered LDH (838.07±101.27 IU/L) and GGT (6.36±0.87 IU/L) levels, in comparison with the positive and negative controls ($P<0.05$) (Table 1).

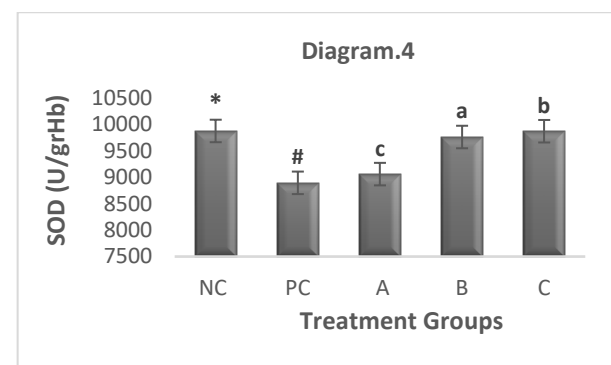
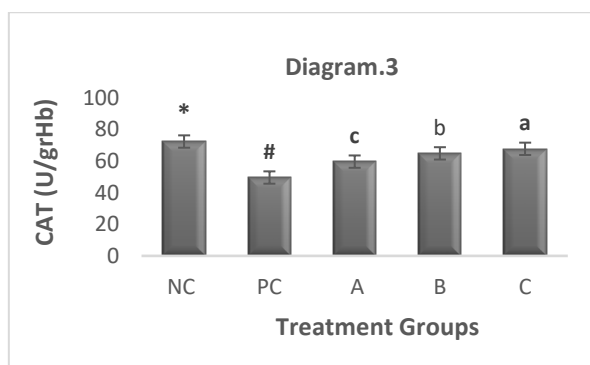
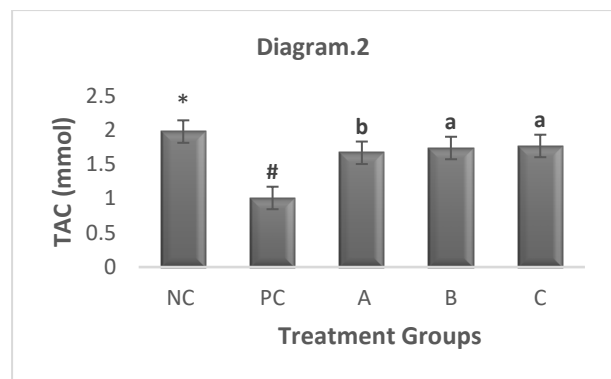
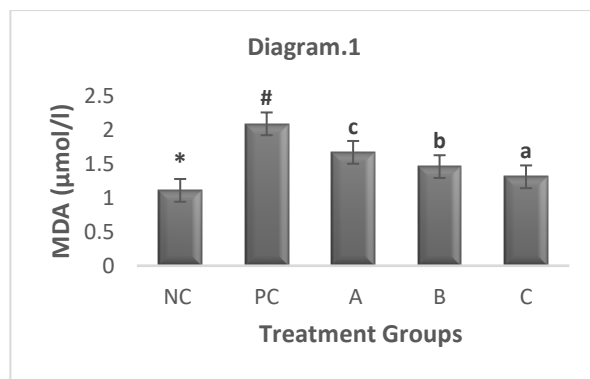
Moreover, the daily gavage of AgNP caused reductions in the levels of serum ALB, Glo, TP, and an elevation in the level of serum Cr and BUN, compared to the negative control. The high (180 mg/kg)

and moderate (60 mg/kg) doses of *Scrophularia striata* extract administered to groups 5 and 4 resulted in higher levels of Alb (3.48 ± 0.6 and 3.21 ± 0.47 mg/dL), Glo (3.3 ± 0.16 and 2.7 ± 0.46 mg/dL), and TP (6.38 ± 0.8 and 6.5 ± 0.57 mg/dL), compared to the positive control and got close to the negative control ($P < 0.05$). The highest dose of *Scrophularia striata* extract (180 mg/kg) diminished BUN (30.48 ± 9.75 mg/dL) and Cr (0.68 ± 0.14 mg/dL) ($P < 0.05$), (Table 1).

Furthermore, the levels of serum TBIL and DBIL increased with a 30-day daily gavage of 200 ppm AgNPs for the positive control, in comparison with the negative control (Table 1). The daily administration of the extract (20, 60, 180 mg/kg) in three treatment groups along with 200 ppm AgNPs caused changes in serum TBIL and DBIL. Based on our results, significant differences were observed between the groups of concentrations 20, 60, and 180 mg/kg, especially at the concentrations of 180 mg/kg with

0.68 ± 0.02 and 0.16 ± 0.01 , in comparison with the positive control with 0.76 ± 0.03 and 0.19 ± 0.02 and the negative control with 0.55 ± 0.04 and 0.11 ± 0.01 ($P < 0.05$) (Table 1).

The administration of 200 ppm AgNPs increased the range of rat serum blood oxidative stress markers in the positive control, compared to the negative control. The findings showed that hepatotoxicity induction with 200 ppm AgNPs led to a decrease in most studied oxidative stress markers, namely TAC, CAT, SOD, and GPx in the positive control group, in comparison with the negative control group (Figure 2). It was observed that the administration of *Scrophularia striata* hydroalcoholic extract along with 200 ppm AgNPs led to significant alterations in groups 3, 4, and 5 in terms of the oxidative markers, mainly CAT, SOD, and GPx, in comparison with the positive and negative control groups ($P < 0.05$) (Figure 2).



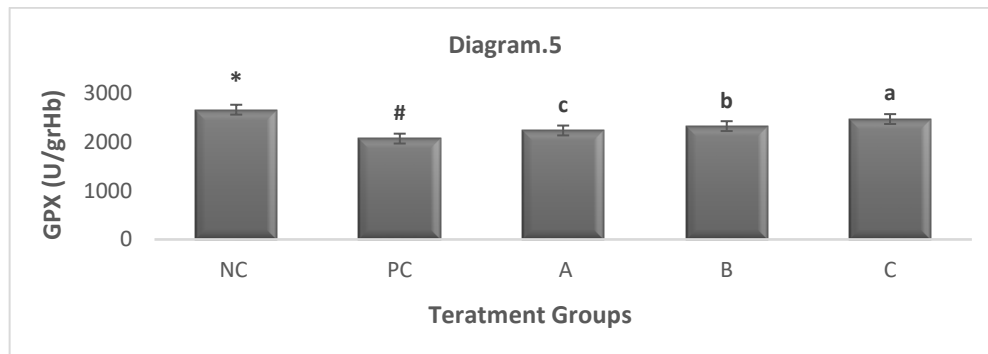


Figure 2. The biochemical modulatory effects of *Scrophularia Striata* extract on blood oxidative stress markers caused by the hepatotoxicity of AgNPs 200 PPM. **Notice:** The values of the small letters **a**, **b** & **c** indicate a significant difference between the studied groups in comparison with the PC # and got close to the NC* groups respectively ($P < 0.05$). NC*: Negative control, PC#: Positive control, A: 20mg/kg, B: 60mg/kg, C: 180mg/kg

Discussion

Deposition of NPs in vital organs, such as the liver causes hepatotoxicity. The liver produces large amounts of a variety of enzymes (Takenaka *et al.*, 2001; Sulaiman *et al.*, 2015). Along with inflammation and damage to the liver cells by AgNPs, hepatic enzymes, serum metabolites, and blood oxidative markers will be out of balance (Markus *et al.*, 2016). Accordingly, the biochemical indices and enzymatic assays are important in tracking the clinical symptoms caused by the toxicity of NPs (Behra *et al.*, 2013; Sturla *et al.*, 2014). Studies have shown that the fresh green parts of *Scrophularia striata* are used in traditional medicine due to the presence of flavonoid compounds (e.g., cinnamic acid, quercetin, isorhamnetin-3-O-rutinoside, nepitrin, and phenylpropanoid glycoside), polyphenolic acid, chlorogenic acid, and various glycoterpenoids with anti-inflammatory properties (Monsef *et al.*, 2010; Mahboubi *et al.*, 2013; Abuajah *et al.*, 2015; Zahiri *et al.*, 2016). Therefore, to assess the impact of *Scrophularia striata* extract on the hepatotoxicity of AgNPs, some liver indicators were evaluated in rat serum.

The inflammatory processes and cell toxicity are accompanied by an imbalance in tissue enzymes and free radical activity (Sardari *et al.*, 2012). Higher production of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) in combination with imbalanced tissue enzymes and lower antioxidants destroys the double bonds of fatty acids, cell membrane proteins, DNA, cell death, and disturbed cellular signaling (Formagio *et al.*, 2013; Kapoor *et al.*, 2019). Hepatocellular inflammation

and any disease that elevates the metabolic activity of the liver could be associated with an acute increase in intracellular enzymes or transaminases (Music *et al.*, 2015; Behzadi *et al.*, 2017). The measurement of four important intracellular liver enzymes, namely ALP, AST, ALT, and LDH are the most common laboratory tests for assessing liver function. These enzymes appear and augment in extracellular fluids after hepatic cell membrane damage with AgNPs due to increased ROS and RNS (Barzegar *et al.*, 2011). To diagnose hepatic diseases, the sensitivity of GGT is higher than ALP and transaminases (AST and ALT). Consequently, the assessment of GGT levels along with LDH and ALP is used to detect the destruction of hepatocytes (Kuriakose *et al.*, 2017; Elias *et al.*, 2018).

Studies demonstrated that green leaf plants which contain antioxidants, such as phenolic acids, flavonoids, and chlorogenic acid prevent imbalance in hepatic enzymes and serum metabolites (e.g., ALT, AST, ALP, LDH, and GGT) by collecting ROS, RNS, and the free radicals of damaged tissues and cells (Blanco *et al.*, 2018; Pandurangan *et al.*, 2015). In the present study, the levels of AST, ALT, ALP, LDH, and GGT, which raised in the positive control group due to the hepatotoxicity of AgNPs, declined dose-dependently in the treatment groups. Accordingly, it was found that the extract could be effective in biochemical changes. The abovementioned results were consistent with the findings of Azadmehr, Khanpour, and Zahiri (Azadmehr *et al.*, 2009; Khanpour *et al.*, 2015; Zahiri *et al.*, 2016).

Moreover, ALB, Glo, and TP represent the rate of protein synthesized by the liver. The normal concentrations of these biomarkers are disrupted in liver injury (Adeyemi *et al.*, 2012; Zhang *et al.*, 2020). The hepatotoxic dose diminished serum ALB, GLO, and Cr levels. The concentrations of these biomarkers (ALB, GLO, and TP) altered in the three treatments groups, compared to the positive control and negative control groups. The latter results were in line with the studies performed by Bahrami, Lay, and Lawal (Bahrami, 2011; Lay *et al.*, 2014; Lawal *et al.*, 2017).

Ammonia contains nitrogen and is produced by the liver. The urea is transported by the blood from the liver to the kidneys. The measurement of BUN and Cr was a part of the serum biochemical profile for diagnosing AgNPs-induced liver damage and evaluating the effectiveness of the extract. The BIL results from the disintegration of hemoglobin by liver cells. The serum levels of this biomarker increase with further destruction of the liver cells and RBCs (Singh *et al.*, 2009; Adeyemi *et al.*, 2012; Tomita *et al.*, 2019). Therefore, serum DBIL and TBIL levels indicate liver activity in the disintegration and excretion of substances. The modulatory effects of *Scrophularia striata* extract were revealed in the levels of these parameters in the treatment groups, compared to the positive control and negative control groups. As a result, BUN, Cr, DBIL, and TBIL concentrations decreased in the treatment groups in a dose-dependent manner. The mentioned results are consistent with other investigations on the impact of *Scrophularia striata* (Kamalipourazad *et al.*, 2016; Falahi *et al.*, 2018; Tamri, 2019).

Free radicals are very active chemically and play an important role in many diseases. The antioxidant defense naturally neutralizes the influences of these radicals (Prior and Wu, 2013; Rocha *et al.*, 2016). As described above, raised production of free radicals, such as ROS and RNS disrupts the natural mechanism of cellular signaling pathways by misbalancing and weakening the antioxidant defense. The increased production of ROS and RNS along with severe oxidative cellular damage cause an elevation in the oxidative stress biomarkers, such as MDA (Tsikas, 2017; Kwon *et al.*, 2021). *Scrophularia striata* extract was found to be effective in the three

treatments groups, in comparison with the positive and negative control groups (Figure 2). Consistent with this result, Mandelkeret indicated the antioxidant activity of this agent that led to MDA reduction (Mandelkeret *et al.*, 2011).

Antioxidant enzymes, including CAT, SOD, and GPx are powerful free radical scavengers. Collaboration between distinct antioxidants provides higher protection against the attack of ROS and RNS (Ndumele *et al.*, 2011). The TAC reflects the total antioxidant activity of the body. Therefore, TAC measurement can provide more information than assessing each antioxidant component individually (Alonso *et al.*, 2014). *Scrophularia striata* extract was observed to affect the level of this parameter in the treatment groups A, B, and C (Figure 2). The latter finding was in line with the results of Shariatzadeh *et al.* (Shariatzadeh *et al.*, 2016).

The accumulation of hydrogen peroxide (H₂O₂) in the cells causes the oxidation of DNA, proteins, and fats resulting in mutation and cell perdition (Ma *et al.*, 2017). The CAT is an antioxidant enzyme involved in the detoxification of H₂O₂ by catalyzing the conversion of two H₂O₂ molecules to oxygen and two molecules of water. The highest levels of CAT are found in the liver, kidneys, and erythrocytes. The measurement of CAT enzyme activity is a standard and reliable way to assess biological samples, such as serum (Hashem, 2014). We observed that the extract influenced the levels of this parameter in the treatment of groups A, B, and C (Figure 2). The results of Hossain *et al.* concerning the antioxidant activity of medicinal plants and CAT changes are congruent with the results of the current study (Hossain *et al.*, 2014).

Superoxide is a byproduct of the secondary metabolism of oxygen and the lack of control can cause different damages to cells. The SOD is the first and most important antioxidant enzyme in all aerobic organisms that are directly involved in the reduction of reactive oxygen metabolites. This enzyme catalyzes the superoxide and H₂O₂ produced in the cell to an oxygen molecule (O₂). Consequently, the SOD is a remarkable antioxidant present in almost all the cells exposed to oxygen (Markus *et al.*, 2016).

Moreover, GPx is an enzyme with peroxidase activity and plays an important biological role in

protecting organisms against oxidative damage. This enzyme prevents the formation of free radicals by reducing H₂O₂ and a wide range of organic peroxides (Adedara *et al.*, 2018). Therefore, evaluating the activity of the GPx enzyme can be a diagnostic tool for inflammatory and cellular liver damage caused by the toxic effects of AgNPs. There are reports of oxidative stress markers imbalances due to the hepatotoxic impacts of AgNPs similar to the present investigation (Ali *et al.*, 2013; Nasser *et al.*, 2009; Hassan *et al.*, 2019; Majid *et al.*, 2009). In this study, the protective effects of *Scrophularia striata* extract against 200 ppm AgNPs were observed in terms of the antioxidant parameters in the treatment groups A, B, and C, which is consistent with the results of Loganayaki and Ahmed regarding antioxidant activity and free radical scavenging (Loganayaki *et al.*, 2013; Ahmed *et al.*, 2019). Therefore, data analysis revealed that altering liver enzymes, serum biochemical metabolites, and oxidative stress factors could probably be attributed to the antioxidants, such as phenolic acids, flavonols, and flavonoids in *Scrophularia striata* (Sun *et al.*, 2018; Silva *et al.*, 2019).

Conclusion

The AgNPs are widely used in various products and can cause toxicity for a variety of organs in living organisms, especially hepatotoxicity along with

alteration in hepatic enzymes, serum biochemical metabolites, and blood oxidative markers. On the other hand, the medicinal plant *Scrophularia striata* with a range of antioxidant properties can be useful as a substitute for chemical compounds. The results of this study demonstrated that the protective effects of the hydroalcoholic extract of *Scrophularia striata* against the hepatotoxicity of AgNPs are most likely due to the presence of flavonoids. However, further investigation is required to elucidate the cellular and molecular signaling pathways involved in the impacts of *Scrophularia striata* extract.

Acknowledgments

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Conflict of Interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content of the paper.

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بررسی اثر محافظتی و تعدیل‌کنندگی بیوشیمیایی عصاره هیدروالکلی تشنه داری (*Scrophularia striata*) به دلیل سمیت کبدی نانوذرات نقره در مدل موش صحرایی

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زمینه مطالعه: نانوذرات نقره (AgNPs) به طور گسترده ای در محصولات مختلف استفاده می‌شود. از طرف دیگر قادر به ایجاد سمیت در ارگانیسم‌های زنده به ویژه تغییرات فاکتورهای بیوشیمیایی و استرس اکسیداتیو در کبد شوند. گیاه *Scrophularia striata* به دلیل داشتن ترکیبات آنتی‌اکسیدانی قدرتمند می‌تواند بر اثر سمیت نانوذرات نقره در نقاط مختلف بدن تأثیر بگذارد.

هدف: هدف از این مطالعه بررسی اثر تعدیل‌کنندگی عصاره هیدروالکلی *Scrophularia Striata* علیه اثرات سمیت کبدی نانوذرات نقره در آنزیم‌های کبدی، برخی از متابولیت‌های بیوشیمیایی سرم (ALT, AST, ALP, LDH, GGT, Alb, GLO, TP, BUN, Cr, BIL.T, BIL.D) و نشانگرهای استرس اکسیداتیو خون (MDA, TAC, CAT, SOD, GPX) در موش‌های صحرایی نر نژاد ویستار بود.

روش کار: ۳۰ سر موش صحرایی نر نژاد ویستار با وزن متوسط 20 ± 200 گرم به‌طور تصادفی در ۵ گروه ۶ تایی به مدت ۳۰ روز تیمار شدند. حیوانات به ترتیب ۲ میلی‌لیتر آب مقطر را در گروه ۱ (شاهد منفی)، ۲۰۰ ppm نانوذرات نقره (دوز سمیت کبدی) در گروه ۲ (شاهد مثبت) و ۶۰، ۲۰ و ۱۸۰ mg/kg عصاره *Scrophularia Striata* ۲۰۰ ppm نانوذرات نقره در گروه‌های ۳، ۴ و ۵ دریافت کردند. ۲۴ ساعت بعد از آخرین تیمار، موش‌ها تحت بیهوشی سبک و مرگ آسان قرار گرفتند.

نتایج: اثرات تعدیل‌کنندگی روی آنزیم‌های کبدی، متابولیت‌های بیوشیمیایی سرم و نشانگرهای استرس اکسیداتیو، به‌طور عمده در GPX و SOD، CAT اختلاف معنی‌داری بین گروه‌ها مورد مطالعه به خصوص در گروه‌های ۴ و ۵ (۶۰ و ۱۸۰ mg/kg) در مقایسه با گروه کنترل مثبت و کنترل منفی نشان دادند ($P < 0.05$).

نتیجه‌گیری نهایی: احتمالاً گیاه *Scrophularia Striata* به دلیل داشتن برخی از ترکیبات ویژه مانند فلاونوئیدها می‌تواند برخی از تغییرات ناشی از عوارض جانبی نانوذرات نقره در بدن را تا حدودی جبران و اصلاح کند.

واژه‌های کلیدی: سمیت کبدی، آنزیم‌های کبدی، استرس اکسیداتیو، نانوذرات، استریاتاسکروفولاریا