UDC 577.121:577.15 doi: https://doi.org/10.15407/ubj94.03.016

FERRIC OXIDE NANOPARTICLES ADMINISTRATION SUPPRESSES ISONIAZID INDUCED OXIDATIVE STRESS IN THE RAT BRAIN TISSUE

H. FARAMARZI[1], J. SAFFARI-CHALESHTORI[2], S. ZOLGHADRI[3], M. BEHESHTROO[4], A. FARAMARZI[5], S. M. SHAFIEE[4,6]✉

[1]Department of Community Medicine, Faculty of Medicine, Shiraz University of Medical Sciences, Iran;
[2]Clinical Biochemistry Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran;
[3]Department of Biology, Jahrom Branch, Islamic Azad University, Jahrom, Iran;
[4]Department of Biochemistry, Shiraz Branch, Islamic Azad University, Shiraz, Iran;
[5]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;
[6]Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz Iran;
✉e-mail: shafieem@sums.ac.ir

Received: 08 November 2021; **Revised:** 27 June 2021; **Accepted:** 29 September 2022

Isoniazid is one of the anti-tuberculosis therapeutic agents capable of causing side effects such as oxidative stress, brain tissue damage and mental disorders. This study aimed to investigate the effect of ferric oxide (Fe_2O_3) nanoparticles administration on isoniazid-induced oxidative stress parameters in rat brain tissue. Forty adult male Wistar rats (200–250 g) were randomly divided into a group with no treatment as control and four experimental groups. Animals of experimental groups received intraperitoneally for 12 days daily saline, 50 mg/kg of isoniazid, 50 mg/kg of isoniazid and 0.2 or 0.4 mg/kg Fe_2O_3 nanoparticles accordingly. The activity of catalase (CAT), superoxide dismutase (SOD), glutathione-S-transferase (GST), the level of glutathione (GSH), malondialdehyde (MDA) and total protein were determined in brain tissue homogenates by spectrophotometric methods. It was shown that CAT and GST activities, as well as GSH and MDA levels in the brain tissue of animals in the isoniazid-treated group were increased compared with the control untreated group, while following the treatment with 0.2 or 0.4 mg/kg Fe_2O_3 nanoparticles the studied oxidative stress parameters returned to the control level ($P < 0.05$). No changes in SOD activity in any of the treated groups were observed compared to the control. This study showed that the administration of ferric oxide nanoparticles can suppress isoniazid-induced oxidative stress in the brain tissue of rats mentally damaged by isoniazid.

K e y w o r d s: isoniazid, ferric oxide nanoparticles, oxidative stress parameters, brain tissue.

Isoniazid, as a well-known anti-tuberculosis therapeutic agent, has toxic properties which induce some metabolic and morphologic disorders [1]. Heart, liver, and kidney disorders are the most common side effects of treatments with isoniazid [2-4]. However, brain disorders induced by the inflammation and apoptosis in cerebral cortex tissue cause severe cognitive impairment [5].

Oxidative damage, as the worst effect of isoniazid on tissues, occurs from reactive oxygen species (ROS) [6]. These ROSs result in the formation of lipids peroxide that leads to cell membrane damage [7]. Oxidative stress, which is induced by releasing the ROSs, increases the activity of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione-S-transferase (GST), to moderate the ROSs [8, 9]. Moreover, the ROSs led to an increase in malondialdehyde (MDA) and glutathione (GSH) concentrations by inducing lipid peroxidation [10, 11]. Considerable evidence suggests that lipid peroxidation contributes to synaptic dysfunction and neuronal degeneration in brain tissue [12]. In addition, oxidative stress plays an important role in brain injury and tissue damage. The generation of oxidative stress leads to mitochondrial dysfunction, lipid peroxidation, and oxidation of pro-

teins and DNA in brain tissue. As a result, neuronal cell death takes place and people start facing some serious disabilities [13].

There are many antioxidants such as vitamins, medicinal plants, and nutritional supplements that ameliorate oxidative stress [13-16]. Nowadays, nanoparticles have been shown as new important interferers in biological systems [17]. Although, in some cases and depending on their structures, nanoparticles have demonstrated cell toxicity, most of them with antioxidant properties may improve vascular dysfunction associated with hypertension, diabetes mellitus, or atherosclerosis [18]. Some studies demonstrated the potential cytotoxicity of iron-based nanoparticles but they have potential implications in medicine, chemistry, and biology [19, 20]. Ferric oxide (Fe_2O_3) nanoparticles enhance hydrogenase enzyme activity and electron transfer. Therefore, they facilitate the growth of hydrogen-producing bacteria and richness [21]. Nevertheless, some Fe_2O_3 nanoparticles cause hemolysis inhibition of mammalian erythrocytes via their antioxidant effects [22].

It seems that the antioxidant properties of Fe_2O_3 nanoparticles can induce protective effects against oxidative stress [23, 24]. This study investigated the neuroprotective and antioxidant effects of Fe_2O_3 nanoparticles, on isoniazid-induced neurotoxicity rats.

Material and Method

Animals and reagents. The Wistar rats were obtained from Pasteur Institute of Iran, Isoniazid and Fe_2O_3 nanoparticles were purchased from (Sigma-Aldrich Corp., MI, USA). Ethylenediaminetetraacetic acid (EDTA), sodium cyanide, nitro blue tetrazolium, and other chemical reagents were purchased from (Merck, Germany).

Treatment the animals. In this study, 40 adult male Wistar rats weighing 200–250 g were housed in a temperature of 22 ± 2°C and the humidity of 50 ± 5% controlled room with 12 h of light/dark cycle. They were kept for a week for adaptation to the environment before the start of the experiments. A standard diet and tap water were provided *ad libitum.*

All tests and manipulations were conducted according to the guidelines of Institutional Animal Care and the Medical Ethics Committee of Shiraz University of Medical Sciences. There are 5 groups and each group contains 8 rats;

Negative control group: animals (n = 8) received distilled water daily and normal food for 12 days. Sham group: animals (n = 8) received normal saline (isoniazid solvent) intraperitoneally daily for 12 days. Positive control group: animals (n = 8) received 50 mg/kg isoniazid intraperitoneally daily for 12 days. Treated group 1: animals (n = 8) received 50 mg/kg isoniazid intraperitoneally daily and Fe_2O_3 nanoparticle at a dose of 0.2 mg/kg BW for 12 days. Treated group 2: animals (n = 8) received 50 mg/kg isoniazid intraperitoneally daily and Fe_2O_3 nanoparticle at a dose of 0.4 mg/kg BW for 12 days.

In this study, dead animals were excluded. All animals were sacrificed 24 h after the last INH treatment, and their brain tissue was removed quickly and washed out with ice-cold 0.9% saline solution. The tissues were homogenized and powdered by liquid nitrogen (LN2) and stored at -70°C. Then, 50 mg of the powdered brain tissue was homogenized in ice-cold phosphate buffer pH = 7.2, 10 mM and centrifuged at 20,000 g for 10 min at 4°C. The supernatant solution was used immediately for the evaluation of biochemical parameters.

Determination of glutathione-S-transferase (GST) activity. To determine the GST activity, we used the spectrophotometric method that has been described by Habig et al [25].

Briefly, 0.015 g of the powdered tissue in 1 ml of normal saline was added to 150 µl of 1-chloro-2,4-dinitrobenzene (CDNB) (20 µM) as the substrate, 150 µl of glutathione (20 mM), and 2.5 ml of NaH_2PO_4 (0.1 M) buffer. The conjugation is accompanied by an increase in absorbance at 340 nm. The rate of increase was directly proportional to the GST activity in the sample.

Determination of catalase (CAT) activity. Catalase (CAT) enzyme activity was determined according to the Aebi method [26]. The reaction mixture contained enzyme extract (0.015 g tissue powdered and 1 ml normal saline), 100 mM potassium phosphate buffer (pH 7.0), and 10 ml of 30% H_2O_2. The reaction was initiated by the addition of H_2O_2 and the absorbance was measured at 240 nm. One unit of CAT was defined as the amount of enzyme catalyzing the decomposition of 1 mmol of H_2O_2 per minute. The specific activity was calculated based on the units per mg (unit/mg) of protein [26].

Determination of superoxide dismutase (SOD) activity. SOD converts the superoxide anion into hydrogen peroxide and oxygen. The SOD activity was measured according to the Worthington method. Briefly, 0.1 M of EDTA in 0.3 mM of sodium cyanide and 1.5 mM of nitroblue tetrazolium (NBT) was added to the sample in a tube and vortexed for 5 min

on ice. Then, 0.12 mM of riboflavin in 0.067 M potassium phosphate buffer (pH = 7.0-8.0) was added and placed at room temperature for 30 min. Absorption at a λ 560 nm was read within 5 min, and specific activity was calculated based on the units per μg (unit/μg) of protein [27].

Determination of total protein. The protein content was measured using the Bradford method [28]. Briefly, 150 μl of the sample (0.015 g tissue powdered in 2.5 ml normal saline) was added to 600 μl of Bradford solution. Then, 2.25 ml of normal saline was added and incubated for 10 min at room temperature. Subsequently, the absorbance of the solution was measured at λ 595 nm. A series of different dilutions i.e. 30, 60, 90, 120, and 150 μg/ml of BSA was prepared as a standard calibration curve.

Determination of glutathione (GSH). Glutathione is an antioxidant that protects cell components from ROS was determined by the Ellman method [29].

Briefly, 0.02 g of the powdered tissue in 1 ml KH_2PO_4 0.1 M was added to 200 μl of TCA 10% and was centrifuged at 5000 g for 10 min. Subsequently, 100 μl of supernatant was added to 100 μl of acid benzoic nitro- 2 dithiobis (DTNB) (30 mM). The absorbance was measured at λ 240 nm after 10 min. A series of five different dilutions i.e. 10-20 mM GSH was prepared as a standard calibration curve.

Determination of malondialdehyde (MDA). Lipid peroxidation was assessed using MDA level measurement by the Satoh method [30]. According to this method, 0.015 g of the powdered tissue in 2.5 ml normal saline was added to 2.4 ml of TCA (20%) and was centrifuged at 4000 g for 10 min. Afterward, 2 ml of supernatant was added to 2.7 ml of TBA (%0.86) and stored at 100ºC for 30 min. Subsequently, 2.4 n-butanol was added and centrifuged at 4000 g for 15 min. The absorbance of the supernatant was measured at 532 nm. A series of different dilutions i.e. 2.5, 5, 10, 20, 30, 40, 50, and 60 μM of 1,1,3,3 Tetra Epoxy Propane (TEP) was prepared as a standard calibration curve.

Statistical analysis. All data were analyzed by SPSS software version 20 (SPSS Inc., Chicago, IL, USA). The data were analyzed between the groups by One way ANOVA and Tukey's post hoc multicomparison. All results were shown as means ± SD. The *P*-value of less than 0.05 was considered significant.

Results

As shown in Fig. 1 (I), brain GST enzyme activity in the treated rats with isoniazid (50 mg/kg) has increased significantly ($P < 0.05$) in comparison with control and sham group. This significant increase has also been observed in the treated group by 50 mg/kg isoniazid along with 0.2 mg/kg Fe_2O_3 nanoparticle. The brain GST enzyme activity decreased in the treated group by 50 mg/kg of isoniazid with 0.4 mg/kg Fe_2O_3 nanoparticle in comparison with the treated group by 50 mg/kg of isoniazid and the treated group by isoniazid (50 mg/kg) with 0.2 mg/kg Fe_2O_3 nanoparticle. Nevertheless, the brain GST enzyme activity increased in the treated group by 50 mg/kg isoniazid with 0.4 mg/kg Fe_2O_3 nanoparticle in comparison with the control and sham groups.

Isoniazid dose of 50 mg/kg led to an increase in the brain CAT enzyme activity significantly ($P < 0.05$) in comparison with control and sham groups (Fig. 1(II)). However, brain CAT activity has decreased significantly in treated rats with 50 mg/kg isoniazid, 0.2, and 0.4 mg/kg Fe_2O_3 nanoparticle in comparison with treated rats with 50 mg/kg isoniazid ($P < 0.05$). Moreover, the brain CAT enzyme activity had no significant changes in treated groups with 50 mg/kg isoniazid with 0.2, and 0.4 mg/kg Fe_2O_3 nanoparticle compared to control and sham groups. Actually, brain CAT activity decreased significantly ($P < 0.05$) in the treated group with 50 mg/kg isoniazid with 0.2, and 0.4 mg/kg Fe_2O_3 nanoparticle in comparison with the treated group with 50 mg/kg isoniazid.

As shown in Fig. 2 (I), SOD activity did not increase significantly in treated rats with 50 mg/kg isoniazid in comparison with control and sham groups. SOD activity has not changed in treated rats with 50 mg/kg isoniazid and 0.2 mg/kg Fe_2O_3 nanoparticle compared with treated rats with 50 mg/kg isoniazid. However, SOD activity has decreased in treated rats with 50 mg/kg isoniazid and 0.2 mg/kg Fe_2O_3 nanoparticle in comparison with treated rats with 50 mg/kg isoniazid.

GSH concentration (μM) has increased in the treated group by isoniazid (50 mg/kg) significantly ($P < 0.05$) (Fig. 3 (I)). However, GSH concentration decreased in the treated group by 50 mg/kg isoniazid with 0.2 mg/kg Fe_2O_3 nanoparticle in comparison

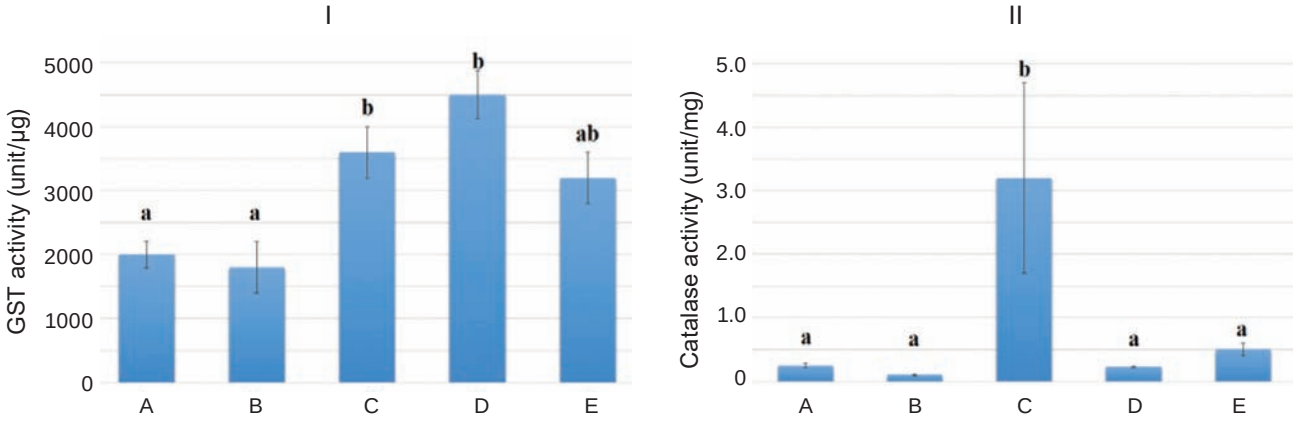

Fig. 1. ***I)*** *Brain GST activity.* ***II)*** *Brain catalase activity. A) The negative group. B) The sham group, C) The positive group that is the group treated with 50 mg/kg isoniazid, D) The group treated with 50 mg/kg isoniazid and 0.2 mg/kg Fe_2O_3 nanoparticle, and E) The group treated with 50 mg/kg isoniazid and 0.4 mg/kg Fe_2O_3 nanoparticle. All data are shown as means ± SD. The groups with the same letter (a, b) are not significant (P < 0.05)*

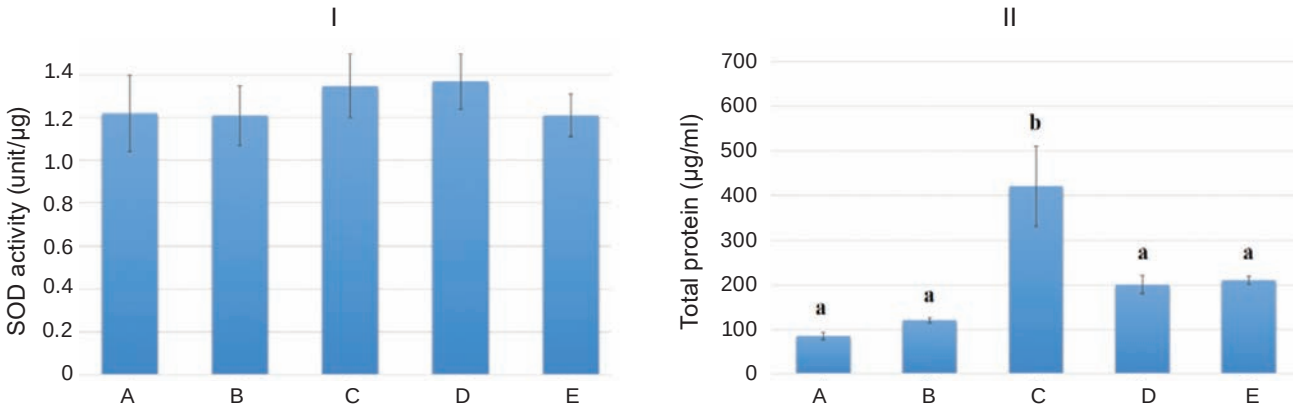

Fig. 2. ***I)*** *Brain SOD activity.* ***II)*** *Total protein. A) The negative group. B) The sham group, C) The positive group that is the group treated with 50 mg/kg isoniazid, D) The group treated with 50 mg/kg isoniazid and 0.2 mg/kg Fe_2O_3 nanoparticle, and E) The group treated with 50 mg/kg isoniazid and 0.4 mg/kg Fe_2O_3 nanoparticle. All data are shown as means ± SD. The groups with the same letter (a) are not significant (P < 0.05)*

with the treated group by 50 mg/kg isoniazid significantly ($P < 0.05$). Nevertheless, elevation of the GSH concentration in the treated group by 50 mg/kg isoniazid with 0.2 mg/kg Fe_2O_3 nanoparticle was significant ($P < 0.05$) in comparison with the control and sham groups. Conversely, GSH concentration decreased in the treated group by 50 mg/kg isoniazid with 0.4 mg/kg Fe_2O_3 nanoparticle and was equal to the control and sham groups.

MDA, as the most common criterion to determine the amount of lipid peroxidation, has increased in the treated group by 50 mg/kg isoniazid significantly ($P < 0.05$) in comparison with the control and sham groups. Fig. 3 (II), shows that the amount of lipid peroxidation (MDA) has decreased in the treated groups by 50 mg/kg isoniazid with 0.2 and 0.4 mg/kg Fe_2O_3 nanoparticle significantly ($P < 0.05$) in comparison with the treated group by 50 mg/kg isoniazid.

Discussion

The brain, by low antioxidant capacity and high oxygen consumption, is exposed to severe oxidative stress damage [31, 32]. Some studies have revealed that some drugs or other compounds can induce oxidative stress and brain injury [33]. Isoniazid, as the first step in the treatment and prophylaxis of tuberculosis, induces oxidative stress and tissue dama-

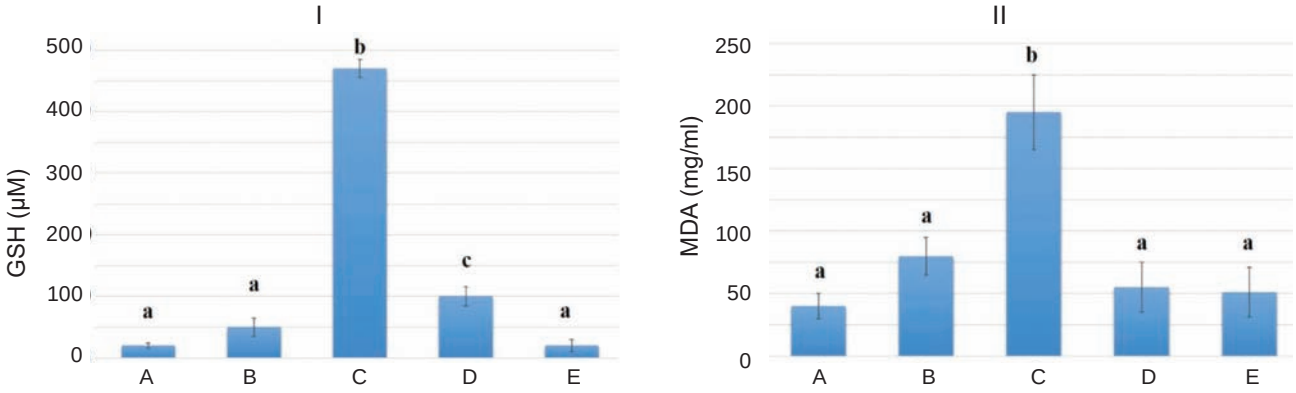

*Fig. 3. **I)** Brain GSH. **II)** Brain MDA. A) The negative group. B) The sham group, C) The positive group that is the group treated with 50 mg/kg isoniazid, D) The group treated with 50 mg/kg isoniazid and 0.2 mg/kg Fe_2O_3 nanoparticle, and E) The group treated with 50 mg/kg isoniazid and 0.4 mg/kg Fe_2O_3 nanoparticle. All data are shown as means ± SD. The groups with the same letter (a) are not significant ($P < 0.05$)*

ge [34]. Previous studies have shown that isoniazid leads to mitochondrial dysfunction in the liver and brain by induction of oxidative stress [35, 36]. Actually, there is ample evidence that isoniazid increases the susceptibility of *Mycobacterium tuberculosis* by inhibiting the enzyme enoyl [acyl carrier protein] reductase and oxidative stress enhancement [37, 38]. Therefore, most of the neurotoxicity effects of isoniazid induce *via* increasing oxidative stress [39].

The results of this study showed that the administration of 50 mg/kg isoniazid can induce oxidative stress in rats leading to brain damage. The recent studies have demonstrated that antioxidants and some natural products have the potential to be the best defense against tissues that are damaged by inhibitory effects on oxidative stress [40], Abrahams et al. showed the antioxidant effects of curcumin on models of neurodegeneration, aging, and oxidative stress [41] and Samarghandian et al. showed that carnosol has protective effects against oxidative stress that induces brain damage in rats [42].

In recent years, nanoparticles are known as novel antioxidants that protect against some oxidative stress damage [43]. Metal-based nanoparticles including iron oxide have beneficial roles in management of diseases regarding their antioxidant effects [44, 45]. In the present study the antioxidant role of ferric oxide nanoparticles against isoniazid induced neurotoxicity was studied via the evaluation of several markers of the oxidative stress.

The results of this study showed that brain GST enzyme activity increases after treating the rats with 50 mg/kg isoniazid though it moderates by treating 0.2 and 0.4 mg/kg Fe_2O_3 nanoparticles (Fig. 1 (I)). Mohan et al. showed that crude sulfated polysaccharide has the protective effect against oxidative stress caused by isoniazid in the liver, kidney, and brain of adult Swiss albino rats by the moderation of GST [46]. Previous studies showed that some nanoparticles such as zinc oxide nanoparticles improved the effect of vitamin E and C on GST in liver cells [47].

Increased CAT activity in the treated rats by 50 mg/kg isoniazid (Fig. 1 (II)) confirms that isoniazid can induce oxidative stress that is in line with previous studies such as Sunarsih et al [48]. However, decreased CAT activity in the treated rats by 50 mg/kg isoniazid with 0.2 and 0.4 mg/kg Fe_2O_3 nanoparticle indicates that ferric oxide treatment leads to the ROSs accumulation which subsequently leads to decreasing of the CAT activity. Chirra et al. showed that the carbodiimide chemistry-based bioconjugation leads to decrease in catalase activity, while the carbodiimide chemistry-based bioconjugation with gold nanoparticles can lead to more catalase activity [49]. Also Zhang et al. showed that TiO_2 nanoparticles can affect the structure of catalase enzyme directly and increase its activity [50].

The SOD activity of the rats' brain had no significant change after treating with 50 mg/kg isoniazid or treating with 50 mg/kg isoniazid with 0.2 and 0.4 mg/kg Fe_2O_3 nanoparticle (Fig. 2(I)). This can be related to low SOD enzyme activity in the brain compared with other tissues such as the liver [51].

A sharp increase of GSH in the treated rats by 50 mg/kg isoniazid (Fig. 3 (I)) and a significant decrease of GSH in the treated rats by 50 mg/kg isoniazid with 0.2 and 0.4 mg/kg Fe_2O_3 nanoparti-

cle revealed that ferric oxide nanoparticles play an important role in the protection of damage induced by oxidative stress via decreasing of GSH. Alkaladi et al. showed that zinc oxide nanoparticles lead to decreasing the GSH levels in liver and gills tissues [47]. Reduced glutathione GSH leads to increase in the solubility of the xenobiotics via GST catalytic activity [52, 53]. Thus it seems that the existence of nanoparticles in cells leads to the activation of GST and consumption of GSH.

A significant increase in the MDA concentration in treated rats with 50 mg/kg isoniazid (Fig. 3 (II)) shows that isoniazid is a potent oxidant that induces hyper peroxidation in biological lipids. Actually, increasing of MDA concentration in these rats indicates the higher production of free radicals [54]. In this study, ferric oxide nanoparticles caused a significant decrease of MDA in the treated rats by 50 mg/kg isoniazid with 0.2 and 0.4 mg/kg Fe_2O_3 nanoparticles (Fig. 3 (II)). Some nanoparticles such as TiO_2 induce lipid peroxidation [55]. In the present research ferric oxide has improved the lipid peroxidation in the treated rats by 50 mg/kg isoniazid. He et al. showed that some nanoparticles such as nano Fe_2O_3 and nano MgO can decrease lipid peroxidation and promote cell growth at low concentrations in green algae [56]. Similarly, Behera et al. indicated that nano-Fe as a feed additive can improve the hematological and immunological parameters of fish and moderate the stress oxidative factors [57]. Because of, this study was done on brain tissues of rats and determined some antioxidant factors and related enzymes it seems that, it is necessary to conduct more studies on the expression of genes and proteins involved in oxidative stress. Altogether, further studies are needed to confirm the ameliorative effects of Fe_2O_3 nanoparticles on the neurotoxicity of isoniazid.

Conclusion. Isoniazid, as the most important anti-tuberculosis agent, induces oxidative stress and tissue damage. Because of its sensitivity and its properties, the brain tissue is more exposed to stress oxidative damage than other tissues. This study showed that ferric oxide nanoparticles can improve the oxidative stress parameters on isoniazid-induced stress oxidative in brain damaged rats. However, there is a need for more experimental studies such as *in vivo* and *in vitro* studies to confirm these results.

Acknowledgments. We would like to thank Seyed Mohammad Jafari in the Research Consultation Center of Shiraz University of Medical Sciences for editing the English language of the manuscript.

Author contributions. Hossein Faramarzi, Ali Faramarzi and Samaneh Zolghadri, performed the experiments; Javad Saffari-Chaleshtori, drafted the manuscript; Mojtaba Beheshtroo, analyzed the data; Sayed Mohammad Shafiee designed the experiments, oversaw the project and finalize the manuscript with inputs from all the authors.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This study was funded by the Research and Technology Deputy of Shiraz University of medical sciences, Shiraz, Iran, based on the research grant number: 12048.

ВВЕДЕННЯ НАНОЧАСТИНОК ОКСИДУ ЗАЛІЗА ПРИГНІЧУЄ ІНДУКОВАНИЙ ІЗОНІАЗИДОМ ОКСИДАТИВНИЙ СТРЕС У ТКАНИНІ МОЗКУ ЩУРІВ

H. Faramarzi[1], J. Saffari-Chaleshtori[2], S. Zolghadri[3], M. Beheshtroo[4], A. Faramarzi[5], S. M. Shafiee[4,6]✉

[1]Department of Community Medicine, Faculty of Medicine, Shiraz University of Medical Sciences, Iran;
[2]Clinical Biochemistry Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran;
[3]Department of Biology, Jahrom Branch, Islamic Azad University, Jahrom, Iran;
[4]Department of Biochemistry, Shiraz Branch, Islamic Azad University, Shiraz, Iran;
[5]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran;
[6]Autophagy Research Center, Shiraz University of Medical Sciences, Shiraz Iran;
✉e-mail: shafieem@sums.ac.ir

Ізоніазид є одним із протитуберкульозних засобів, здатних спричиняти такі побічні ефекти, як оксидативний стрес, пошкодження тканин мозку та психічні розлади. Це дослідження мало на меті визначити вплив наночастинок оксиду заліза (Fe_2O_3) на параметри оксидативного стресу, індукованого ізоніазидом, у тканині мозку щурів. Сорок дорослих самців щурів Wistar (200–250 г) були випадковим чином розділені на контрольну (без лікування) та чотири експериментальні групи. Тварини дослідних груп отримували внутрішньоочеревинно протя-

гом 12 діб щоденно фізіологічний розчин, 50 мг/кг ізоніазиду, 50 мг/кг ізоніазиду та 0,2 або 0,4 мг/кг наночастинок Fe_2O_3 відповідно. У гомогенатах тканин головного мозку спектрофотометричними методами визначали активність каталази (CAT), супероксиддисмутази (SOD), глутатіон-S-трансферази (GST), рівень глутатіону (GSH), малонового діальдегіду (MDA) і загального протеїну. Показано, що активність CAT і GST, а також рівні GSH і MDA в тканинах мозку тварин у групі лікування ізоніазидом були підвищені порівняно з контрольною групою, тоді як після додавання 0,2 або 0,4 мг/кг наночастинок Fe_2O_3 досліджувані показники оксидативного стресу повернулися до контрольного рівня ($P < 0,05$). Активність SOD у жодній із оброблених груп не змінювалась порівняно з контролем. Це дослідження показало, що введення наночастинок оксиду заліза може пригнічувати індукований ізоніазидом оксидативний стрес у тканині мозку щурів, психічно пошкоджених ізоніазидом.

Ключові слова: ізоніазид, наночастинки оксиду заліза, параметри оксидативного стресу, тканина головного мозку.

References

1. Campanerut-Sá PA, Ghiraldi-Lopes LD, Meneguello JE, Fiorini A, Evaristo GP, Siqueira VL, Scodro RB, Patussi EV, Donatti L, Souza EM, Cardoso RF. Proteomic and morphological changes produced by subinhibitory concentration of isoniazid in *Mycobacterium tuberculosis*. *Future Microbiol*. 2016; 11(9): 1123-1132.
2. Ni J, Wang H, Wei X, Shen K, Sha Y, Dong Y, Shu Y, Wan X, Cheng J, Wang F, Liu Y. Isoniazid causes heart looping disorder in zebrafish embryos by the induction of oxidative stress. *BMC Pharmacol Toxicol.* 2020; 21(1): 22.
3. Sivannan S, Vishnuvardhan A, Elumalai K, Srinivasan S, Eluri K, Elumalai M, Muthu R. Isoniazid-induced liver disorder in the treatment of tuberculosis. *Chronic Dis Transl Med*. 2018; 4(4): 268-270.
4. Apalowo O, Musa S, Asaolu F, Apata J, Oyedeji T, Babalola O. Protective Roles of Kolaviron Extract from Garcinia kola Seeds against Isoniazid-induced Kidney Damage in Wistar Rats. *Eur J Med Plants*. 2019; 26(4): 1-8.
5. Ruan LY, Fan JT, Hong W, Zhao H, Li MH, Jiang L, Fu YH, Xing YX, Chen C, Wang JS. Isoniazid-induced hepatotoxicity and neurotoxicity in rats investigated by 1 H NMR based metabolomics approach. *Toxicol Lett.* 2018; 295: 256-269.
6. Georgieva N, Gadjeva V, Tolekova A. New isonicotinoylhydrazones with SSA protect against oxidative-hepatic injury of isoniazid. *TJS*. 2004; 2(1): 37-43.
7. Leutner S, Eckert A, Müller WE. ROS generation, lipid peroxidation and antioxidant enzyme activities in the aging brain. *J Neural Transm (Vienna).* 2001; 108(8-9): 955-967.
8. Nandi A, Yan LJ, Jana CK, Das N. Role of Catalase in Oxidative Stress- and Age-Associated Degenerative Diseases. *Oxid Med Cell Longev*. 2019; 2019: 9613090.
9. Mazur-Bialy AI, Kozlowska K, Pochec E, Bilski J, Brzozowski T. Myokine irisin-induced protection against oxidative stress *in vitro*. Involvement of heme oxygenase-1 and antioxidazing enzymes superoxide dismutase-2 and glutathione peroxidase. *J Physiol Pharmacol*. 2018; 69(1): 117-125.
10. Song Q, Liu L, Yu J, Zhang J, Xu M, Sun L, Luo H, Feng Z, Meng G. Dihydromyricetin attenuated Ang II induced cardiac fibroblasts proliferation related to inhibitory of oxidative stress. *Eur J Pharmacol*. 2017; 807: 159-167.
11. Wang LL, Yu QL, Han L Ma XL, Song RD, Zhao SN, Zhang WH. Study on the effect of reactive oxygen species-mediated oxidative stress on the activation of mitochondrial apoptosis and the tenderness of yak meat. *Food Chem*. 2018; 244: 394-402.
12. Raefsky SM, Furman R, Milne G, Pollock E, Axelsen P, Mattson MP, Shchepinov MS. Deuterated polyunsaturated fatty acids reduce brain lipid peroxidation and hippocampal amyloid β-peptide levels, without discernable behavioral effects in an APP/PS1 mutant transgenic mouse model of Alzheimer's disease. *Neurobiol Aging*. 2018; 66: 165-176.
13. Khatri N, Thakur M, Pareek V, Kumar S, Sharma S, Datusalia AK. Oxidative Stress: Major Threat in Traumatic Brain Injury. *CNS Neurol Disord Drug Targets*. 2018; 17(9): 689-695.
14. Sepidarkish M, Farsi F, Akbari-Fakhrabadi M, Namazi N, Almasi-Hashiani A, Maleki

Hagiagha A, Heshmati J. The effect of vitamin D supplementation on oxidative stress parameters: A systematic review and meta-analysis of clinical trials. *Pharmacol Res.* 2019; 139: 141-152.
15. Shingnaisui K, Dey T, Manna P, Kalita J. Therapeutic potentials of *Houttuynia cordata* Thunb. against inflammation and oxidative stress: A review. *J Ethnopharmacol.* 2018; 220: 35-43.
16. Wang W, Kang PM. Oxidative stress and antioxidant treatments in cardiovascular diseases. *Antioxidants (Basel).* 2020; 9(12): 1292.
17. Mihu MR, Cabral V, Pattabhi R, Tar MT, Davies KP, Friedman AJ, Martinez LR, Nosanchuk JD. Sustained nitric oxide-releasing nanoparticles interfere with methicillin-resistant *Staphylococcus aureus* adhesion and biofilm formation in a rat central venous catheter model. *Antimicrob Agents Chemother.* 2016; 61(1): e02020-16.
18. Mauricio MD, Guerra-Ojeda S, Marchio P, Valles SL, Aldasoro M, Escribano-Lopez I, Herance JR, Rocha M, Vila JM, Victor VM. Nanoparticles in Medicine: A Focus on Vascular Oxidative Stress. *Oxid Med Cell Longev.* 2018; 2018: 6231482.
19. Paunovic J, Vucevic D, Radosavljevic T, Mandić-Rajčević S, Pantic I. Iron-based nanoparticles and their potential toxicity: Focus on oxidative stress and apoptosis. *Chem Biol Interact.* 2020; 316: 108935.
20. Burello E, Worth AP. A theoretical framework for predicting the oxidative stress potential of oxide nanoparticles. *Nanotoxicology.* 2011; 5(2): 228-235.
21. Zhang J, Fan C, Zhang H, Wang Z, Zhang J, Song M. Ferric oxide/carbon nanoparticles enhanced bio-hydrogen production from glucose. *Int J Hydrogen Energy.* 2018; 43(18): 8729-8738.
22. Bhattacharya K, Gogoi B, Buragohain AK, Deb P. Fe_2O_3/C nanocomposites having distinctive antioxidant activity and hemolysis prevention efficiency. *Mater Sci Eng C Mater Biol Appl.* 2014; 42: 595-600.
23. Abbasi BA, Iqbal J, Mahmood T, Qyyum A, Kanwal S. Biofabrication of iron oxide nanoparticles by leaf extract of Rhamnus virgata: characterization and evaluation of cytotoxic, antimicrobial and antioxidant potentials. *Appl Organomet Chem.* 2019; 33(7): e4947.
24. Abdullah JAA, Eddine LS, Abderrhmane B, Alonso-González M, Guerrero A, Romero A. Green synthesis and characterization of iron oxide nanoparticles by pheonix dactylifera leaf extract and evaluation of their antioxidant activity. *Sustainable Chem Pharm.* 2020; 17: 100280.
25. Habig WH, Pabst MJ, Jakoby WB. Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. *J Biol Chem.* 1974; 249(22): 7130-7139.
26. Aebi H. Catalase *in vitro. Methods Enzymol.* 1984; 105: 121-126.
27. Winterbourn CC, Hawkins RE, Brian M, Carrell RW. The estimation of red cell superoxide dismutase activity. *J Lab Clin Med.* 1975; 85(2): 337-341.
28. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem.* 1976; 72(1-2): 248-254.
29. Siegers CP, Riemann D, Thies E, Younes M. Glutathione and GSH-dependent enzymes in the gastrointestinal mucosa of the rat. *Cancer Lett.* 1988; 40(1): 71-76.
30. Satoh K. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. *Clin Chim Acta.* 1978; 90(1): 37-43.
31. Shohami E, Beit-Yannai E, Horowitz M, Kohen R. Oxidative stress in closed-head injury: brain antioxidant capacity as an indicator of functional outcome. *J Cereb Blood Flow Metab.* 1997; 17(10): 1007-1019.
32. Spiotta AM, Stiefel MF, Gracias VH, Garuffe AM, Kofke WA, Maloney-Wilensky E, Troxel AB, Levine JM, Le Roux PD. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *J Neurosurg.* 2010; 113(3): 571-580.
33. Abdel-Rahman M, Rezk MM, Ahmed-Farid OA, Essam S, Abdel Moneim AE. Saussurea lappa root extract ameliorates the hazards effect of thorium induced oxidative stress and neuroendocrine alterations in adult male rats. *Environ Sci Pollut Res Int.* 2020; 27(12): 13237-13246.
34. Verma AK, Yadav A, Singh SV, Mishra P, Rath SK. Isoniazid induces apoptosis: Role of oxidative stress and inhibition of nuclear translocation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2). *Life Sci.* 2018; 199: 23-33.

35. Ahadpour M, Eskandari MR, Mashayekhi V, Haj Mohammad Ebrahim Tehrani K, Jafarian I, Naserzadeh P, Hosseini MJ. Mitochondrial oxidative stress and dysfunction induced by isoniazid: study on isolated rat liver and brain mitochondria. *Drug Chem Toxicol.* 2016; 39(2): 224-232.
36. Chowdhury A, Santra A, Bhattacharjee K, Ghatak S, Saha DR, Dhali GK. Mitochondrial oxidative stress and permeability transition in isoniazid and rifampicin induced liver injury in mice. *J Hepatol*. 2006; 45(1): 117-126.
37. de Ávila MB, Bitencourt-Ferreira G, de Azevedo WF. Structural basis for inhibition of enoyl-[acyl carrier protein] reductase (InhA) from *Mycobacterium tuberculosis. Curr Med Chem*. 2020; 27(5): 745-759.
38. Bulatovic VM, Wengenackv, Uhl JR, Hall L, Roberts GD, Cockerill FR 3rd, Rusnak F. Oxidative stress increases susceptibility of Mycobacterium tuberculosis to isoniazid. *Antimicrob Agents Chemother.* 2002; 46(9): 2765-2771.
39. Çelik H, Kucukler S, Çomaklı S, Caglayan C, Özdemir S, Yardım A, Karaman M, Kandemir FM. Neuroprotective effect of chrysin on isoniazid-induced neurotoxicity via suppression of oxidative stress, inflammation and apoptosis in rats. *Neurotoxicology.* 2020; 81: 197-208.
40. Lee MT, Lin WC, Yu B, Lee TT. Antioxidant capacity of phytochemicals and their potential effects on oxidative status in animals - A review. *Asian-Australas J Anim Sci*. 2017; 30(3): 299-308.
41. Abrahams S, Haylett WL, Johnsonv G, Carr JA, Bardien S. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. *Neuroscience*. 2019; 406: 1-21.
42. Samarghandian S, Azimi-Nezhad M, Borji A, Samini M, Farkhondeh T. Protective effects of carnosol against oxidative stress induced brain damage by chronic stress in rats. *BMC Complement Altern Med*. 2017; 17(1): 249.
43. Kumar H, Bhardwaj K, Nepovimova E, Kuča K, Dhanjal DS, Bhardwaj S, Bhatia SK, Verma R, Kumar D. Antioxidant Functionalized Nanoparticles: A Combat against Oxidative Stress. *Nanomaterials (Basel).* 2020; 10(7): 1334.
44. Younis NK, Ghoubaira JA, Bassil EP, Tantawi HN, Eid AH. Metal-based nanoparticles: Promising tools for the management of cardiovascular diseases. *Nanomedicine*. 2021; 36: 102433.
45. Dou J, Li L, Guo M, Mei F, Zheng D, Xu H, Xue R, Bao X, Zhao F, Zhang Y. Iron Oxide Nanoparticles Combined with Cytosine Arabinoside Show Anti-Leukemia Stem Cell Effects on Acute Myeloid Leukemia by Regulating Reactive Oxygen Species. *Int J Nanomedicine*. 2021; 16: 1231-1244.
46. Mohan MSG, Ramakrishnan T, Mani V, Achary A. Protective effect of crude sulphated polysaccharide from *Turbinaria ornata* on isoniazid rifampicin induced hepatotoxicity and oxidative stress in the liver, kidney and brain of adult Swiss albino rats. *Indian J Biochem Biophys.* 2018;55:237-244.
47. Alkaladi A. Vitamins E and C ameliorate the oxidative stresses induced by zinc oxide nanoparticles on liver and gills of *Oreochromis niloticus. Saudi J Biol Sci*. 2019; 26(2): 357-362.
48. Sunarsih ES, Anggraeny EN, Wibowo PSL, Elisa N. Phytochemical Screening and Antioxidant Activity of Strawberry Juice (Fragaria ananassa Duchessne) Against Ureum Level, Creatinin, and Enzyme Catalase Activity In Isoniazid-Induced Wistar Male Rats. *STRADA Jurnal Ilmiah Kesehatan.* 2020; 9(2): 1595-604.
49. Chirra HD, Sexton T, Biswal D, Hersh LB, Hilt JZ. Catalase-coupled gold nanoparticles: comparison between the carbodiimide and biotin-streptavidin methods. *Acta Biomater.* 2011; 7(7): 2865-2872.
50. Zhang HM, Cao J, Tang BP, Wang YQ. Effect of TiO_2 nanoparticles on the structure and activity of catalase. *Chem Biol Interact.* 2014; 219: 168-174.
51. Danh HC, Benedetti MS, Dostert P. Differential changes in superoxide dismutase activity in brain and liver of old rats and mice. *J Neurochem.* 1983; 40(4): 1003-1007.
52. Mofeed J, Mosleh YY. Toxic responses and antioxidative enzymes activity of *Scenedesmus obliquus* exposed to fenhexamid and atrazine, alone and in mixture. *Ecotoxicol Environ Saf.* 2013; 95: 234-240.
53. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiol Rev.* 2014; 94(2): 329-354.

54. Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. *Anal Biochem*. 2017; 524: 13-30.
55. Runa S, Lakadamyali M, Kemp ML, Payne CK. TiO_2 Nanoparticle-Induced Oxidation of the Plasma Membrane: Importance of the Protein Corona. *J Phys Chem B*. 2017; 121(37): 8619-8625.
56. He M, Yan Y, Pei F, Wu M, Gebreluel T, Zou S, Wang C. Improvement on lipid production by *Scenedesmus obliquus* triggered by low dose exposure to nanoparticles. *Sci Rep*. 2017; 7(1): 15526.
57. Behera T, Swain P, Rangacharulu P, Samanta M. Nano-Fe as feed additive improves the hematological and immunological parameters of fish, *Labeo rohita* H. *Appl Nanosci*. 2014; 4(6): 687-694.