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ADVERSE EFFECTS OF IRON OXIDE NANOPARTICLES ON SOME BIOCHEMICAL MARKERS AND AMELIORATIVE EFFECT OF SILYMARIN

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ABSTRACT : Fe_2O_3 nanoparticles are used in many biomedical implementations. However, research on their toxicity remains insufficient. Therefore, this study aimed to ascertain the damages that these nanoparticles may cause to some biochemical markers, as well as to assess the ameliorative role of silymarin. This study was tested on thirty-two rats, which were distributed into four groups. The first contained control rats, the second included rats poisoned with iron oxide nanoparticles, the third contained rats poisoned with nanoparticles and were given silymarin, and the fourth included rats that received silymarin only. Biochemical analyzes were performed, which included assessment of the serum levels of some hepatic and renal parameters. The results confirmed a significant augmentation in ALT and AST levels in rats poisoned with nanoparticles compared to the control. Also, the serum levels of all parameters were significantly improved when poisoned rats received silymarin. This study concluded that the use of silymarin significantly ameliorated the biochemical disturbances induced by iron oxide nanoparticles.

Key words : Iron oxide nanoparticles, toxicity, biochemical parameters.

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INTRODUCTION

The application of nanotechnology in medicine has revolutionized healthcare because of its unique potential for developing pathological diagnoses as well as pharmacological treatments (Trivedi *et al*, 2022 and Ahmed *et al*, 2022). Iron oxide nanoparticles (Fe_2O_3-NPs) are magnetic nanoparticles that possess unique electromagnetic and optical properties, which make them desirable in many medical and pharmaceutical applications such as gene cloning, drug delivery, and DNA separation (Badawi *et al*, 2022; Sidkey, 2020 and Danthanarayana *et al*, 2018). In contrast, the beneficial properties of nanoparticles were offset by harmful effects depending on the concentration of the doses (Mahmoud *et al*, 2022; Kakoty *et al*, 2022; Ramadhan and Ghareeb, 2021). Until the present time, natural herbs are preferred to be used for medicinal purposes by many people in order to avoid the side effects of industrial medicines (Al-Haidari *et al*, 2021). Silymarin (SLM) is an extractor from the seeds of *S. marianum*, which is of the *Asteraceae* family (Aziz *et al*, 2021).

In addition to its anti-inflammatory properties, it well-deservedly possesses liver-protecting properties by acting as an antioxidant and detoxifying. SLM counteracts harmful free radicals caused by the decomposition of toxic substances (Dwivedi *et al*, 2022; Boukazoula and Ayari, 2022). Therefore, this substance is sold in the pharmacopoeia of many countries (Chaitanya *et al*, 2022). It is used to treat hepatic and toxic diseases as it can prevent liver dysfunction (Mukhtar *et al*, 2021). Some experimental research also reported on the positive effects of SLM in nephrotoxic drugs in laboratory animals, especially its effects on kidney function (Aktas and Bayram, 2020; Shahbazi *et al*, 2012 and Turgut *et al*, 2008). The current study aimed to evaluate the harmful effectiveness Fe_2O_3-NPs on some biochemical markers in experimental rats, as well as to estimate the potential enhancing role of silymarin.

MATERIALS AND METHODS

Nanoparticles and silymarin products

The dispersion of Fe_2O_3 nanoparticles was used with the following specifications (Fig. 1): APS: 20-100 nm, purity: 99.9%, form: liquid, color: brown, pH value: 5-7, surface treatment compound: carboxylate, concentration: 20 wt% and dispersing agent: water (ddH2O). As for its

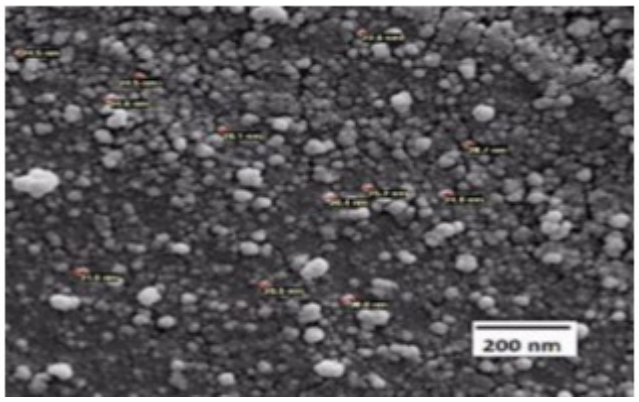

Fig. 1 : SEM – Fe_2O_3 NPs.

properties, they were as follows: UV absorption, high transparency, durability, excellent thermal stability, high hardness, and excellent optical. It was acquired from Nanoshel LLC, Wilmington, USA. Also, Pure Silymarin Envelopes, dietary supplement (made in USA) were used.

Study design

Thirty-two male albino rats, their ages ranged between 17-25 weeks were used, while their weight ranged between 185-230 g. They were obtained from animal houses within Iraqi universities. They were placed inside cages of suitable capacity designated for them under appropriate laboratory conditions in terms of temperature, lighting, and ventilation. They were allowed easy oncoming to water and feed. One week before the start of the experimental study, these rats were adapted to laboratory conditions.

Equally, all laboratory animals were distributed into 4 groups as explained in Table 1. After completing the fourteenth day of the study, the anesthetized rats were sacrificed and blood was drawn from them by puncturing the hearts.

For biochemical analysis purposes, hepatic and renal serum enzymes were measured using diagnostic kits in an automatic machine.

Statistical analysis

Data were statistically processed by Graph Pad Prism 7. To determine the variation between experimental groups, one-way analysis of variance (ANOVA) and then Tukey's post hoc test were performed. Significant difference was considered at P value ≤ 0.05.

RESULTS

The results of the biochemical evaluation confirmed a clear statistical augmentation in the levels of ALT (245.06±7.68) and AST (361.31±7.26) for Fe_2O_3-NPs group when compared with CON group (91.52±6.86 and 139.15±5.47). As for the other biochemical indicators ALP, BU and Cr their levels increased in rats poisoned with nanoparticles, but not significantly when compared with untreated animals. On the other hand, SLM treatment significantly reduced the levels of all perturbed parameters in the Fe_2O_3-NPs + SLM group compared to the Fe_2O_3-NPs group as presented in Table 1.

DISCUSSION

An overall recognition of the quantitative localization of nanoparticles in different tissues of the body helps to map the pharmacokinetics of nanomedicine, so data obtained from *in vivo* toxicity studies of Fe_2O_3-NPs is an essential ingredient for a succeeded transit to the clinical framing (Patil *et al*, 2015). The results confirmed that iron oxide nanoparticles with APS between 20-100 nm and carboxylate surface treatment compound had obvious toxic effects on some biochemical parameters, especially on hepatic enzymes ALT and AST. Metal oxide NPs induce cytotoxicity by releasing ions, depending on several main factors that determine their toxicity such as size, shape, surface area and charge, oxidation state, and other physicochemical properties (Sengul and Asmatulu, 2020; Karlsson *et al*, 2022). Elevated levels of these parameters are indicative of impaired liver function (Ghareeb, 2022). Our findings are consistent with another study conducted by Feng *et al* (2018), when they systematically investigated the toxicity of commercially available iron oxide NPs in different sizes and coatings. They found that all these NPs tended to proliferate in the liver, that their biolysis and removal of iron oxide NPs in the hepatic tissue was comparatively late. Besides, these nanoparticles tended to be trapped in smaller amounts in the kidneys. In a previous study by Sadeghi and Espanani (2015), they found that iron oxide nanoparticles administered to lab rats via pulmonary inhalation penetrated the circulation, quickly reached the liver and created serious inflammation in the liver tissue, and also observed the penetration of hepatic enzymes into the blood serum as a result of damaged liver cells. In another

Table 1 : Study groups and doses.

Groups	Daily treatments for up to 2 weeks
CON	Laboratory rats without any treatment.
Fe_2O_3-NPs	Laboratory rats were injected with Fe_2O_3-NPs (40 mg/kg) intra-peritoneally (Rahdar *et al*, 2018).
Fe_2O_3-NPs+ SLM	Rats exposed to Fe_2O_3-NPs were provided with SLM (100 mg/kg) via a gastric tube (Ghareeb, 2021).
SLM	Rats were provided with SLM (100 mg/kg) only.

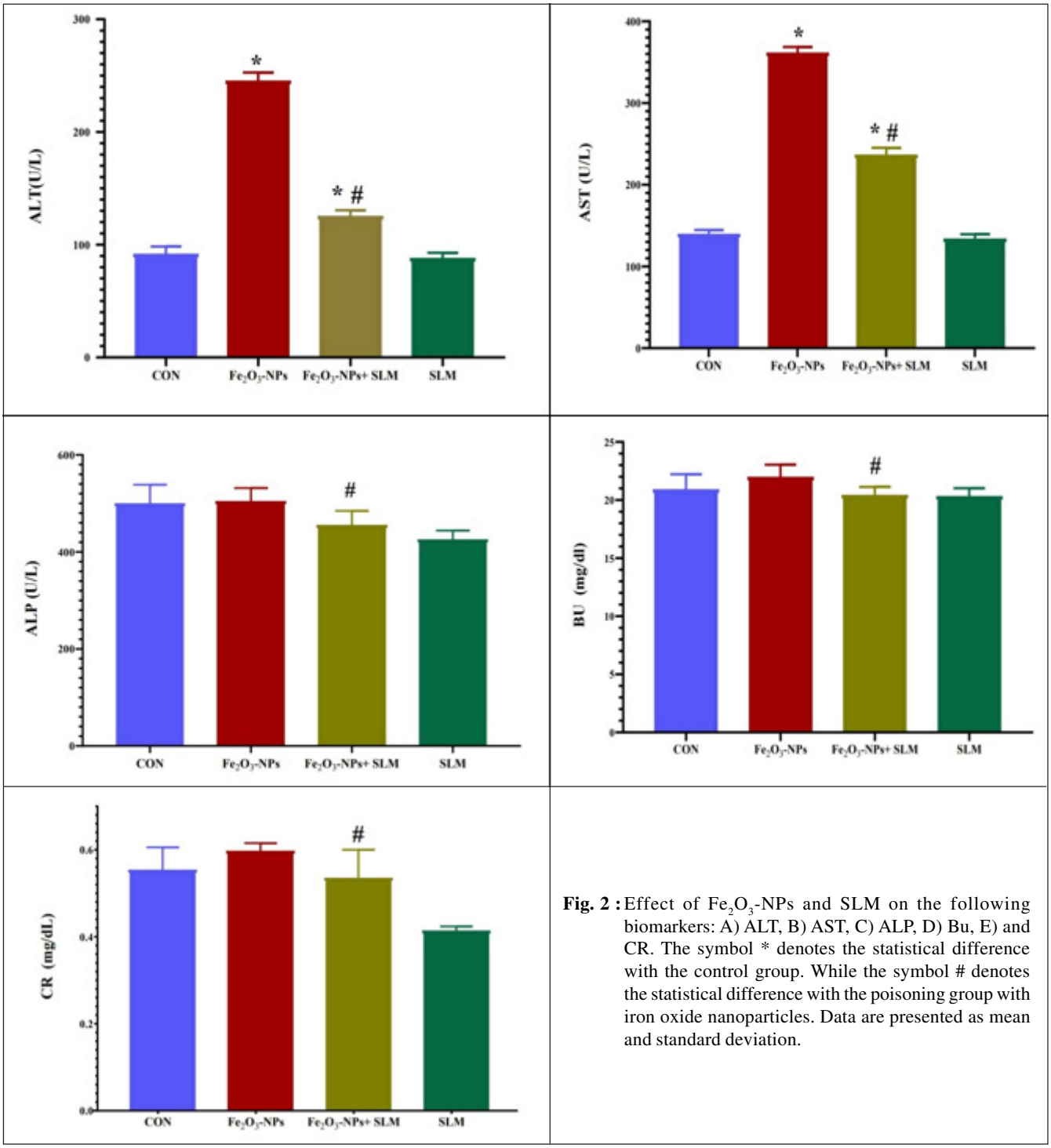

Fig. 2 : Effect of Fe_2O_3-NPs and SLM on the following biomarkers: A) ALT, B) AST, C) ALP, D) Bu, E) and CR. The symbol * denotes the statistical difference with the control group. While the symbol # denotes the statistical difference with the poisoning group with iron oxide nanoparticles. Data are presented as mean and standard deviation.

context, supplementing the rats with silymarin led to a significant modification of all the negative changes induced in the serum biochemical parameters. This may be due to the protective activity of SLM against toxic factors to the liver and kidneys, as well as chemicals (Fanoudi *et al*, 2020). Silymarin exerts a positive effect on hepatocytes by binding to the receptors of the liver cell membrane responsible for absorbing toxins, thus stopping the cell's absorption of toxins. In addition, it stimulates protein synthesis and thus regenerates liver cells (Khazaei *et al*, 2022). In another recent study by Lamia *et al* (2021), they found that administration of silymarin to ovariectomized rats significantly reduced the infiltration of inflammatory cells as well as the damage to liver and kidney tissues caused by carbon tetrachloride. They concluded that SLM might be advantageous as a curative intervention to preserve liver and kidney health.

CONCLUSION

Our results indicated that iron oxide nanoparticles had a clear detrimental effect on the liver biochemical parameters ALT and AST, which indicated a disturbance in the liver function, while its effect on the renal biochemical parameters was less. Supplementing nanoparticles-exposed rats with silymarin led to a significant improvement in all the affected biochemical parameters.

REFERENCES

Ahmed F F, Ghareeb O A and Al-Bayti A A (2022) Nephro defensive efficiency of *Cichorium intybus* against toxicity caused by copper oxide nanoparticles. *Pak. J. Med. Hlth Sci.* **16**(3), 542-545.

Aktas I and Bayram D (2020) Investigation of the effects of silymarin on valproic acid-induced kidney damage in rats. *Harran Üniversitesi Veteriner Fakültesi Dergisi* **9**(1), 42-48.

Al-Haidari K A, Faiq T N and Ghareeb O A (2021) Preventive value of black seed in people at risk of infection with COVID–19. *Pak. J. Med. Hlth Sci*. **15**(1), 384-387.

Aziz M, Saeed F, Ahmad N, Ahmad A, Afzaal M, Hussain S, Mohamed A A, Alamri M S and Anjum F M (2021) Biochemical profile of milk thistle (*Silybum marianum* L.) with special reference to silymarin content. *Food Sci. Nutr*. **9**(1), 244-250.

Badawi A, Alharthi S S, Althobaiti M G and Alharbi A N (2022) The effect of iron oxide content on the structural and optical parameters of polyvinyl alcohol/graphene nanocomposite films. *J. Vinyl and Additive Tech.* **28**(1), 235-246.

Boukazoula F and Ayari D (2022) Effect of milk thistle (*Silybum marianum*) supplementation on the serum levels of oxidative stress markers in male half marathon athletes. *Biomarkers* **21**, 1-4.

Chaitanya M V, Ali H S and Usamo F B (2022) Regulatory considerations of herbal biomolecules. In : *Herbal Biomolecules in Healthcare Applications*. Jan 1 (pp. 669-676). Academic Press.

Danthanarayana A N, Manatunga D C, De Silva R M, Chandrasekharan N V and Nalin De Silva K M (2018) Magnetofection and isolation of DNA using polyethyleneimine functionalized magnetic iron oxide nanoparticles. *Royal Society open Sci*. **5**(12), 181369.

Dwivedi P S, Patil V S, Khanal P, Bhandare V V, Gurav S, Harish D R, Patil B M and Roy S (2022) System biology-based investigation of Silymarin to trace hepatoprotective effect. *Computers in biology and medicine* **6**, 105223.

Fanoudi S, Alavi M S, Karimi G and Hosseinzadeh H (2020) Milk thistle (*Silybum marianum*) as an antidote or a protective agent against natural or chemical toxicities: a review. *Drug Chem. Toxicol.* 43(3), 240-254.

Feng Q, Liu Y, Huang J, Chen K, Huang J and Xiao K (2018) Uptake, distribution, clearance and toxicity of iron oxide nanoparticles with different sizes and coatings. *Scientific Reports* **8**(1), 1-3.

Ghareeb O A (2022) Hepato-Renal dysfunctions induced by Gold nanoparticles and preservative efficacy of black seed oil. *J. Medicinal Chem. Sci.* **5**(1), 137-143.

Ghareeb O A (2021) Toxicopathological effects of zinc oxide nanoparticles on the liver function and preventive role of silymarin *in vivo*. *Indian J. Forensic Med. Toxicol*. **15** (2), 3212-3217.

Kakoty V, Sarathlal K C, Pandey M, Dubey S K, Kesharwani P and Taliyan R (2022) Biological toxicity of nanoparticles. In : *Nanoparticle Therapeutics*. Jan 1 (pp. 603-628), Academic Press.

Karlsson H L, Toprak M S and Fadeel B (2022) Toxicity of metal and metal oxide nanoparticles. In : *Handbook on the Toxicology of Metals.* Jan 1 (pp. 87-126). Academic Press.

Khazaei R, Seidavi A and Bouyeh M (2022) A review on the mechanisms of the effect of silymarin in milk thistle (*Silybum marianum*) on some laboratory animals. *Vet. Med. Sci.* **8**(1), 289-301.

Lamia S S, Emran T, Rikta J K, Chowdhury N I, Sarker M, Jain P, Islam T, Gias Z T, Shill M C and Reza H M (2021) Coenzyme Q10 and silymarin reduce CCl_4-induced oxidative stress and liver and kidney injury in ovariectomized rats—implications for protective therapy in chronic liver and kidney diseases. *Pathophysiology* **28**(1), 50-63.

Mahmoud J H, Ghareeb O A and Mahmood Y H (2022) The role of garlic oil in improving disturbances in blood parameters caused by zinc oxide nanoparticles. *J. Medicinal and Chem. Sci.* **5**(1), 76-81.

Mukhtar S, Xiaoxiong Z, Qamer S, Saad M, Mubarik M S, Mahmoud A H and Mohammed O B (2021) Hepatoprotective activity of silymarin encapsulation against hepatic damage in albino rats. *Saudi J. Biolog. Sci.* **28**(1), 717-723.

Patil U S, Adireddy S, Jaiswal A, Mandava S, Lee B R and Chrisey D B (2015) *In vitro/in vivo* toxicity evaluation and quantification of iron oxide nanoparticles. *Int. J. Mole. Sci.* **16**(10), 24417-50.

Rahdar A, Taboada P, Aliahmad M, Hajinezhad M R and Sadeghfar F (2018) Iron oxide nanoparticles: Synthesis, physical characterization and intraperitoneal biochemical studies in Rattus norvegicus. *J. Mole. Struct*. **1173**, 240-245.

Ramadhan S A and Ghareeb O A (2021) Toxicity of AgNPs upon liver function and positive role of *Tinospora cordifolia*: *In Vivo*. *Pak. J. Med. Hlth Sci*. **15**(6), 2164- 2166.

Sadeghi L and Espanani H R (2015) Toxic effects of the Fe_2O_3 nanoparticles on the liver and lung tissue. *Bratislavske lekarske listy* **116**(6), 373-8.

Sengul A B and Asmatulu E (2020) Toxicity of metal and metal oxide nanoparticles: a review. *Environ. Chem. Lett*. **18**(5), 1659-1683.

Shahbazi F, Dashti-Khavidaki S, Khalili H and Lessan-Pezeshki M (2012) Potential renoprotective effects of silymarin against nephrotoxic drugs: a review of literature. *J. Pharm. Pharmaceut. Sci.* **15**(1), 112-123.

Sidkey N (2020) Biosynthesis, characterization and antimicrobial activity of iron oxide nanoparticles synthesized by fungi. *Al-Azhar J. Pharmaceut. Sci*. **62**(2), 164-179.

Trivedi R, Upadhyay T K, Kausar M A, Saeed A, Sharangi A B, Almatroudi A, Alabdallah N M, Saeed M and Aqil F (2022) Nanotechnological interventions of the microbiome as a next-generation antimicrobial therapy. *Sci. Total Environ*. **6**, 155085.

Turgut F, Bayrak O, Catal F, Bayrak R, Atmaca A F, Koc A, Akbas A, Akcay A and Unal D (2008) Antioxidant and protective effects of silymarin on ischemia and reperfusion injury in the kidney tissues of rats. *Int. Urol. Nephrol*. **40**(2), 453-460.