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Sub-acute Effects of α-Fe_2O_3 Nanoparticles on Some Biochemical Parameters in Mice

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ABSTRACT

The goal of the study was to find out the toxic effect of daily treatment with α-Fe_2O_3 nanoparticles for 14 and 28 days on some biochemical indicators in mice by measuring ferritin, transferrin, cholinesterase enzyme activity, the concentration of Caspase-3, and the concentration of glutathione and malondehyde in brain and liver tissues at doses of 75, 150 and 300 mg/kg. α-Fe2O3 nanoparticles at the dose of 75 mg/kg caused a significant decrease in the activity of the acetyl cholinesterase enzyme in the brain and liver after 14 days of treatment, compared with the control group and the doses of α- Fe_2O_3 (75, 150, and 300 mg/kg) led to a significant decrease in the activity of the acetyl cholinesterase enzyme in the brain after 28 days of treatment. Fe_2O_3 at a dose of 75 mg/kg on the 14th day and at a dose of 150 mg/kg on the 28th day of treatment resulted in a significant increase in the caspase-3 enzyme in the brain compared to the control group. While the doses of 150 and 300 mg/kg for 28 days led to a significant increase in transferrin concentration compared with the control group, The α-Fe_2O_3 nanoparticles at doses of 75, 150, and 300 mg/kg for 28 days caused a significant decrease in the concentration of glutathione in the liver and brain tissues compared with the control group, accompanied by a significant increase in the concentration of malondehyde in the brain and liver tissues at doses of 150 and 300 mg/kg of body weight. We conclude that repeated exposure to α - Fe_2O_3 nanoparticles has toxic effects on vital organs such as the brain and liver, represented by a decrease in the concentration of acetylcholinesterase and its ability to induce oxidative stress through a decrease in glutathione concentration and an increase in malondehyde concentration in mice .

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INTRODUCTION

Nanotechnology has huge potential in magnetic resonance imaging and early disease recognition, with specific nano-scale agents being adapted for molecular imaging in the context of magnetic resonance imaging, ultrasound, optical imaging, and X-ray imaging. Magnetic nanoparticles can also be widely used in drug delivery, gene delivery, and targeting **(Indira and Lakshmi, 2010)** and as iron supplements for anaemic patients **(Lu *et al*., 2010).** Iron is an essential cofactor for respiratory chain enzymes as well as for DNA synthesis and cell proliferation **(Rouault and Tong, 2008).** Iron oxide nanoparticles (IONPS) are able to cross the blood-brain barrier and reach the brain **(Wang *et al*., 2010)** and magnetic nanoparticles must be biocompatible and biodegradable with a size ranging from 10 to 100 nanometers because nanoparticles smaller than 10 nanometers are excreted by the kidneys and particles larger than 200 nanometers do not pass through the cell membrane easily and can stimulate the immune system as foreign elements and be excreted outside the body **(Gupta and Gupta, 2005)**.

The biomedical applications of iron oxide magnetic nanoparticles are broader than others due to their biocompatibility, high stability, and ease of use. One of its most important uses is drug delivery **(Liang *et al*., 2008; Espanani *et al*., 2013).** Because the use of these particles in various industries has increased human exposure to them, the investigation of nanoparticles role in cell growth and survival is of greater importance **(Zhu *et al*., 2009).** Human skin, lungs, and gastrointestinal tracts are the most common entry routes for nanoparticles and their pathogens **(Buzea *et al*., 2007)**. Airborne

nanoparticles have high mobility and can be easily inhaled through the respiratory tract **(Yeh *et al*., 2012)**. One of the most common adverse effects of nanoparticles is the emergence of reactive oxygen species (ROS). It is almost certain that all studied nanoparticles produce reactive oxygen species, and it is the main mechanism of nanoparticle toxicity that can lead to enlargement and apoptosis in human and animal tissues (**Miura and Shinohara 2009)**.

The use of nanoparticles, including iron oxide (Fe2O3), has recently increased in various fields, including industrial and medical applications and the production of nano-based drugs. Our current study aimed to reveal the toxic effects of iron oxide nanoparticles (α-Fe_2O_3, 20-40nm) on some biochemical parameters in mice.

MATERIALS AND METHODS

Ethical Approval

In accordance with institutional policies on the care and use of animals in research, we received official clearance for the study protocol from the Committee of Postgraduate Studies at the College of Medicine, University of Mosul, Iraq.

Animals

Forty mice (males and females), white, of Swiss origin, that were raised in the laboratories of the College of Veterinary Medicine at the University of Mosul. The weights of these mice ranged between 25-35 g. The mice were raised in laboratory conditions characterized by a light cycle distributed over 12 hours of light and 12 hours of darkness, and the temperature of the animal house was 22 ± 2 degrees C°. Laboratory food was provided from local factories for the production of animal feed in the city of Mosul.

Preparation of iron oxide particles Fe2O3

The (α-Fe_2O_3) nanoparticles are characterized by a reddish-brown color, a round shape, a purity of 98 +%, and a size of partials 20-40 nm. www.us-nano.com, the required weight of α- Fe_2O_3 nanoparticles were mixed with distilled water at a volume of administration 10 ml/kg of body weight with an ultrasonic 50 Hz device to facilitate the dispersion of particles with water and facilitate swallowing by mice (**Kumari *et al*., 2012;2013; Dhakshinamoorthy *et al*., 2017).**

Experimental design

Forty mice were divided into four groups, 10 /group, and they were administration as follows:

A- The first (control) group were given distilled water at a volume of 10 ml / kg of body weight orally.

B- The second group were given 75 mg/kg iron oxide nanoparticles (α- Fe_2O_3) orally.

C- The third group was given 150 mg/kg iron oxide nanoparticles (α- Fe_2O_3) orally

D- The fourth group was given 300 mg/kg iron oxide nanoparticles (α- Fe_2O_3) orally.

After blood was collected half of mice in each group were killed at the fourteenth in order to isolated brain and liver tissues. The same process was repeated at the 28th day:

1- Estimation of ferritin and transferrin concentration in serum of mice treated with α- Fe_2O_3: The level of ferritin and transferrin in the blood serum were measured in mice treated with α- Fe_2O_3 nanoparticles during 14 and 28 days of oral dosing using kits (Bioassay, China for transferrin and Giesse Diagnostics Srl, Italy).

2- Cholinesterase activity was measured by using electrometric method (**Mohammad *et al*., 2007; Al-zubaidy, *et al*., 2011; Al-zubaidy and Amine., 2018**) **.**

Solutions used: Buffer phosphate solution with a pH of 8.1 and prepared as follows: 0.309 g of sodium barbital, 0.040 g of dihydrogen potassium phosphate and 8.768 g of sodium chloride were added in 225 ml of distilled water, then the pH of the final solution was adjusted to 8.1 Using hydrochloric acid (0.1 M) and measuring the pH with a pH meter, complete the volume to 250 ml by adding distilled water. The aqueous solution of acetylcholine iodide 7.1% was prepared as follows: 0.375 mg of acetylcholine iodide was added in 5 ml of distilled water, and prepared on the same measurement day.

3- Caspase-3 activity in the brain and liver was estimated by using ELISA kit (SunLong Biotech, China), since the optical density is measured by the optical spectrum at the wavelength of 450 nm. The optical density value is proportional to the Casp-3 concentration and the Casp-3 concentration in the samples can be calculated by comparing the OD of the samples to the standard curve.

4- In addition Glutathion and Malondyhayde concentration in brain and liver were measured using modified Ellmann method **(James, 1982)** and method of **(Ohkawa *et al*., 1979)**, respectilly .

Statistical analysis

The results were analyzed statistically using the test of variance One way analysis of variance and Two way analysis of variance, then the results were subjected to the Least significant difference test based on the Sigma plot statistical analysis program, and the level of significant difference for all tests was at the (p) probability level less than 0.05.

RESULTS

1- Effects of α- Fe_2O_3 nanoparticles at doses (75, 150, and 300 mg/kg) on the serum transferrin and ferritin concentration of mice treated on the 14th and 28th day

The treatment of mice with 150 and 300 mg/kg of α- Fe_2O_3 nanoparticles for 28 days led to a significant elevation in transferrin concentration compared with the control group (table 1). While there was no significant change in ferritin concentration in mice's serum (table 2).

Table 1: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150, and 300 mg/kg) on the serum transferrin concentration of mice treated on the 14th and 28th day of dosing

Dose of α- Fe2O3 nanoparticles	Transferrin conc. (ng/ml) 14 days	Transferrin conc. (ng/ml) 28 days
Control distilled water	361.04±16.61	393.92±22.24
75 mg/kg	306.91±16.18	418.92±1901^{C}
150 mg/kg	349.49±21.87	493.56±27.33*^{ad}
300 mg/kg	365.30±28.35	604.16±26.56*^{abc}

* The value differs significantly compared with the control group at a level of ($P \leq 0.05$).

2.Effects of α- Fe2O3 nanoparticals on the cholinesterase activity in the brain and liver by an electrometric method

Treatment of mice with 75,150,300 mg/kg of α- Fe_2O_3 resulted in a significant decrease in the cholinesterase activity of brain and liver tissues after 14 days of treatment, compared to the control group, as shown by the inhibition rates (34.92, 33.33, and 47.46%) in the brain and (38.46, 30.76, and 25 %), respectively, in the liver (table 3).

Table 2: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150, and 300 mg/kg) on the serum ferritin concentration of mice treated on the 14th and 28th day of dosing

Dose of α- Fe2O3 nanoparticles	Ferritin (µ g/l), 14 days	Ferritin (µ g/l), 28 days
Control distilled water	242±2.66	247±1.73
75 mg/kg	248±4.72	264.80±23.70
150 mg/kg	234±15.90	260.20±13.18
300 mg/kg	291±52.10	247.20±6.39

Table 3: Effects of α- Fe_2O_3 at doses (75, 150 and 300 mg / kg) on day 14th of treatment in brain and liver tissues Cholinesterase activity in mice

	Brain 14day		Liver 14day	
Dose of α- Fe_2O_3 nanoparticles	Δ pH /30 min	%inhibition	Δ pH /30 min	%inhibition
Control distilled water	0.63± 0.05	0	0.52± 0.04	0
75 mg/kg	0.41± 0.03*	34.92	0.32± 0.06*	38.46
150 mg/kg	0.42± 0.05*	33.33	0.36± 0.02*	30.76
300 mg/kg.	0.31± 0.09*	47.46	0.39± 0.02*	25

***** The value significantly difference from the control group at a level ($P \leq 0.05$).

Treatment of mice with 75, 150, and 300 mg/kg of α- Fe_2O_3 resulted in a significant decrease in the cholinesterase activity of the brain after 28 days of treatment, compared to the control group, as shown by the inhibition rates of 36.49, 33.78, and 31.08%, respectively, while the rate of inhibition in the liver was 45.68%, caused by the 300 mg/kg dose of α- Fe_2O_3 table (4).

Table 4: Effects of α- Fe_2O_3 at doses (75, 150 and 300 mg / kg on day 28th of treatment in brain and liver tissues cholinesterase activity in mice.

	Brain 28day		Liver 28day	
Dose of α- Fe_2O_3 nanoparticles	Δ pH /30 min	Inhibition%	Δ pH /30 min	Inhibition %
Control distilled water	0.74± 0.06		0.81± 0.09	
75 mg/kg	0.47± 0.08*	36.49	0.66± 0.01	18.52
150 mg/kg	0.49± 0.04*	33.78	0.63± 0.04	22.22
300 mg/kg.	0.51± 0.06*	31.08	0.44± 0.08*	45.68

3. Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 14 and 28 day of treatment on the activity of the caspase-3 enzyme in the brain and liver of mice

Treatment of mice with 75 mg/kg of α- Fe_2O_3 resulted in a significant elevation in the caspase-3 concentration of brain tissue after 14 days of treatment, compared to the control group (table 5). The dose of 150 mg/kg after 28 days of treatment caused a significant elevation in the concentration of brain tissue compared to the control group table (6).

Table 5: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 14th day of dosing on the activity of the caspase-3 enzyme in the brain and liver of mice

Dose of α- Fe_2O_3 nanoparticles	Caspase-3 enzyme in brain and liver (ng/ml) 14 days	
	Brain 14 day	Liver 14 day
Control distilled water	1.16±0.13	1.56±0.26
75 mg/kg	2.33±0.58*A	1.34±0.17
150 mg/kg	1.17±0.11	1.14±0.07
300 mg/kg	0.65±0.32	1.24±0.21

Mean ± SE with various letters in the column means significant at a level of ($P \leq 0.05$).

Table 6: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 28 th day of dosing on the activity of the caspase-3 enzyme in the brain and liver of mice.

Dose of α- Fe_2O_3 nanoparticles	Caspase-3 enzyme in brain and liver (ng/ml) 14 days	
	Brain 14 day	Liver 14 day
Control distilled water	1.10±0.10	1.42±0.05
75 mg/kg	1.05±0.10	1.63±0.30
150 mg/kg	1.88±0.11*¡AB	1.47±0.23
300 mg/kg	1.28±0.26	1.15±0.21

Mean ± SE with various letters in the column means significant at a level of ($P \leq 0.05$).

4. Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 14 and 28 day of dosing on the concentration of glutathione and malondyhyde in the brain and liver of mice

Treatment mice with 75,150,300 mg/kg of α-Fe2O3 resulted in a significant decrease in the concentration of glutathione in brain and liver after14 and 28 days of treatment, compared to the control group table (7,8).

Table 7: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 14th day of dosing on the concentration of glutathione in the brain and liver of mice

Parameter	Brain 14 day		Liver 14 day	
Treatment groups	Glutathione (µmol/g)	Decreasing %	Glutathione (µmol/g)	Decreasing %
Control distilled water	1.20± 0.12		3.27± 0.55	
75 mg/kg	0.21± 0.05*	82.5	1.19± 0.21*	63.61
150 mg/kg	0.23± 0.04*	80.83	1.95± 0.13*	40.37
300 mg/kg	0.26± 0.09*	78.33	1.91± 0.20*	41.59

* The value significantly difference compared with the control group at a level of ($P \leq 0.05$).

Table 8: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 28th day of dosing on the concentration of glutathione in the brain and liver of mice.

Parameter	Brain 28 day		Liver 28 day	
Treatment groups	Glutathione (µmol/g)	Decreasing %	Glutathione (µmol/g)	Decreasing %
Control distilled water	0.64± 0.09		5.17± 0.25	
75 mg/kg	0.41± 0.03*	35.94	2.64± 0.30*	48.94
150 mg/kg	0.52± 0.04	18.75	3.54± 0.17*	31.53
300 mg/kg	0.27± 0.04*AB	57.81	2.32± 0.17*AB	55.13

Treatment mice with 75,150,300 mg/kg of α-Fe_2O_3 resulted in a significant elevation in the concentration of malondyhed in brain and liver after14 and 28 days of treatment, compared to the control group table (9, 10).

Table 9: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) at the 14th day of dosing on the concentration of malondyhade in the brain and liver of mice.

Parameter	Brain 14 day		Liver 14 day	
Treatment groups	Malondialdehyde (µmol/g)	Elevation %	Malondialdehyde (µmol/g)	Elevation %
Control distilled water	209.98± 8.14		231.14± 14.01	
75 mg/kg	314.80± 28.58	49.92	339.46± 29.51	46.86
150 mg/kg	476.42± 86.67*	126.89	331.26± 57.55	43.32
300 mg/kg	565.03± 61.61*A	169.09	351.31± 63.05	51.99

Table 10: Effects of α- Fe_2O_3 nanoparticles at doses (75, 150 and 300 mg/kg) on the 28th day of dosing on the concentration of malondialdehyde in the brain and liver of mice.

Parameter	Brain 28 day		Liver 28 day	
Treatment groups	Malondialdehyde (µmol/g)	Elevation %	Malondialdehyde (µmol/g)	Elevation %
Control distilled water	259.58± 20.26		256.78± 31.50	
75 mg/kg	503.26± 40.81*	93.87	384.07± 70.20	49.57
150 mg/kg	595.31± 96.50*	129.33	414.09± 47.21*	61.26
300 mg/kg	543.50± 64.13*	109.38	453.38± 30.82*	76.56

* The value significantly difference compared with the control group at a level of ($P \leq 0.05$).

DISCUSSION

Magnetic nanoparticles have recently attracted great interest due to their unique physical and chemical properties and potential applications in various biomedical fields **(Lu *et al.*, 2010)**. Among these magnetic nanoparticles, iron oxide nanoparticles, which are characterized by their compatibility, are bioavailable, injectable, and may have a high rate of accumulation in target tissue **(Ito *et al*., 2005).**

Ferritin, in its classic and complex role, is the storage protein for excess iron within living cells that is not used immediately **(Jacobs and Worwood, 1975)**. The amount of ferritin ranges from one-third to three-quarters of the amount of iron in the brain **(Octave *et al.*, 1983) .** There are several reasons to increase serum ferritin, including liver cirrhosis, cancer, and hereditary diseases caused by deficiency of ferritin protein (**Wang *et al*., 2010)** . An increase in iron concentration does not necessarily mean an increase in ferritin concentration **(Loeffler *et al.*, 1995).** Previous research indicates that serum ferritin leaks from damaged cells , including liver cell damage, in other words, an increase in ferritin concentration results from cellular damage, **(Dominguez-Versa *et al.*, 2010)** and it is associated with the formation of free radicals, which results in more cellular damage **(Kell and Pretorius, 2014).**

Our results are consistent with the previous studies by **Kell and Pretorius, (2014) which** showed an increase in iron levels in the brains of Alzheimer's patients compared to normal ferritin levels, i.e., an increase in iron levels without a concomitant change in the level of ferritin **(Halliwell, 1992; 2001)**.

Transferrin is a transporter protein in the blood **(Briley-Saebo *et al*., 2004)**. In the case of saturation of the blood with iron, the haemoglobin stock in the blood increases with an increase in the level of transferrin in the serum. A previous study showed an increase in haemoglobin and transferrin in rats treated with iron oxide nanoparticles in drinking water for ten days **(Elshemy, 2018).** These results are consistent with our results, which showed an increase in the level of transferrin at doses of 150 and 300 mg/kg after 28 days of dosing with Fe_2O_3.

The chemical activity of the acetylcholine-esterase enzyme is demonstrated through the breakdown of the neurotransmitter acetylcholine into choline and acetic acid **(Romano *et al*., 2015)**. An Inhibiting the activity of this enzyme leads to the accumulation of the neurotransmitter acetylcholine in the nerve endings, causing the signs of cholinergic poisoning, muscarinic, nicotinic, and the central nervous system signs **(Lotti, 2010),** and due to the great importance of this enzyme, its activity was measured in the tissues of the brain and liver, as it was found that when iron oxide particles Fe_2O_3- were given in doses (75, 150, and 300) mg/kg by oral dose, the treatment 14 days there was a significant decrease in the enzyme activity in the brain tissue of the treated mice compared with the control group, and a significant decrease in the enzyme activity in the brain tissue of the treated mice on 28 days compared with the control group for all doses. Exposure to iron oxide nanoparticles Fe_2O_3 leads to neuronal degeneration and affects neurobehavior and signs of toxicity (**Wang *et al*., 2007; Zhu *et al*., 2009; Dhakshinamoorthy *et al*.,2017).** Our results were consistent with a previous study in which rats were given iron oxide particles at a dose of (500,1000,200) mg/kg for 60 days.(**Kumari *et al*.,2013).**

The nanoparticles produce reactive oxygen species (ROS), which is the main mechanism that can lead to apoptosis and DNA damage in mice exposed to iron oxide nanoparticles **(Dhakshinamoorthy *et al*., 2017)**. Our results are consistent with what the researchers stated, who indicated that giving iron oxide nanoparticles led to an increase in the level of the caspase-3 enzyme in the mice's brain. The repeated administration of iron oxide nanoparticles leads to the accumulation of iron in the brain, causing the destruction of cellular structures and the fragmentation of DNA. **(Dhakshinamoorthy *et al*., 2017)**. These results can be explained by the fact that apoptosis increases in a dose-dependent manner **(Liu *et al*., 2018)**. Our results indicated that there was no significant effect on the level of the caspase-3 enzyme in liver cells treated for 28 days. The reason is that the liver is one of the dominant organs for the removal of nanoparticles, and it is the first and largest line for phagocytosis of nanoparticles after the spleen **(Lee *et al*., 2010);** this coincides with the study of **Voss *et al*., (2021).**

Nanoparticles pose adverse effects such as oxidative stress, because they may generate oxidants and have the potential to stimulate the generation of ROS. This defect caused by nanoparticles causes, directly or indirectly, the synthesis of free radicals that may lead to cell toxicity **(Nel *et al*., 2006)** and due to a defect in the cell's vital antioxidant defences, the most important of which are glutathione, while measuring it in body tissues such as the brain and liver, it was inferred that oxidative stress occurred, with an imbalance in the level of antioxidant enzymes and glutathione, as these enzymes help in detecting and diagnosing the occurrence of oxidative stress, as the level of glutathione decreases and is accompanied by an increase in the level of malondialdehyde **(Dalle-Donne *et al*., 2006).** Our results indicate that high and continuous doses of iron oxide nanoparticles had an effect on the levels of glutathione and malondialdehyde in brain and liver tissue, and this is consistent with a previous study conducted on rats **(Reddy *et al*., 2017).**

CONCLUSION

From the current study, it is concluded that α-Fe_2O_3 nanoparticles have toxic effects that depend on dose and duration of exposure, and show through transferrin, cholinesterase, and caspase-3 levels, as well as their effects on oxidative stress induction.

Conflicts of interest

The writers certify that they have no relationships that could give rise to conflicts of interest**.**

REFERENCES

Al-ZUBAIDY, M. H., MOUSA, Y.J., HASAN, M.M., and MOHAMMAD, F.K., 2011. Acute toxicity of veterinary and agricultural formulations of organophosphates dichlorvos and diazinon in chicks. Archives of Industrial Hygiene and Toxicology. 62:317-323. http://dx.doi.org/10.2478/10004-1254-62-2011-2139

Al-ZUBAIDY, M.H., and AMIN, S.M., 2018. Cholinesterase inhibition in chicks treated with

manganese chloride. Iraqi Journal of Veterinary Sciences, .32(2). https://doi.org/10.33899/ijvs.2019.153875

BRILEY- SAEBO, K., BJORNERUD, A., GRANT, D., AHLSTROM, H., BERG, T., and KINDBERG, G.M., 2004. Hepatic cellular distribution and degradation of iron oxide nanoparticles following single intravenous injection in rats: implications for magnetic resonance imaging. Cell and Tissue Research, 316, 315–323.https://doi.org/10.1007/s00441-004-0884-8

BUZEA, C., PACHECO, I.I., and ROBBIE, K., 2007. Nano-materials and nanoparticles: sources and toxicity. Biointerphases. 2(4):MR17–MR71. https://doi.org/10.1116/1.2815690

DALLE-DONNE, I., ROSSI, R., COLOMBO, R., GIUSTARINI, D., and MILZANI, A., 2006. Biomarkers of oxidative damage in human disease. Clinical Chemistry, *52*(4), 601–623. https://doi.org/10.1373/clinchem.2005.061408

DHAKSHINAMOORTHY, V., MANICKAM, V., and PERUMAL, E., 2017. Neurobehavioural toxicity of iron oxide nanoparticles in mice. Neurotoxicity Research, 32(2), 187–203. https://doi.org/10.1007/s12640-017-9721-1

DOMINGUEZ-VERSA, J. M., FERNANDEZ, B., and GALVEZ, N., 2010. Native and synthetic ferritins for nanobiomedical applications: recent advances and new perspectives. Future Medicinal Chemistry, 2(4), 609–618. https://doi.org/10.4155/fmc.09.171

ELSHEMY, M. A. 2018. Iron oxide nanoparticles versus ferrous sulfate in treatment of iron deficiency anemia in rats. Egyptian Journal of Veterinary Sciences, 49(2), 103–109. https://doi.org/10.21608/ejvs.2018.3855.1039

ESPANANI, H.R., FAZILATI, M., SADEGHI, L., YOUSEFIBABADI, V., BAKHIANI, S.A.E., and AMRAIE, E., 2013. Investigation the zinc oxide nanoparticle's effect on sex hormones and cholesterol in rat. International Research Journal of Biological Sciences, 2(8), 54–58. https://doi.org/10.1093/nutrit/nuv059

GUPTA, A. K., and GUPTA, M., 2005. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials, 26(18), 3995–4021. https://doi.org/10.1016/J.BIOMATERIALS.2004.10.012

HALLIWELL, B. 1992. Oxygen radicals as key mediators in neurological disease: fact or fiction? Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 32(S1), S10–S15. https://doi.org/10.1002/ana.410320704

HALLIWELL, B. 2001. Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs & Aging, 18, 685–716.https://doi.org/10.2165/00002512-200118090-00004

INDIRA, T.K., and LAKSHMI, P.K., 2010. Magnetic nanoparticles–a review. International Journal of Pharmaceutical Sciences and Nanotechnology, 3(3), 1035–1042 .https://doi.org/10.3109/21691401.2015.1014093

ITO, A., SHINKAI, M., HONDA, H., and KOBAYASHI, T., 2005. Medical application of functionalized magnetic nanoparticles. Journal of Bioscience and Bioengineering, 100(1), 1–11. https://doi.org/10.1263/jbb.100.77

JACOBS, A., and WORWOOD, M., 1975. Ferritin in serum: clinical and biochemical implications. New England Journal of Medicine, 292(18), 951–956. https://doi.org/10.1056/nejm197505012921805

JAMES, L. R. 1982. Aggregation bias in estimates of perceptual agreement. Journal of Applied Psychology, 67(2), 219. https://doi.org/10.1037/0021-9010.67.2.219

KELL, D. B., and PRETORIUS, E., 2014. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics, 6(4), 748–773. https://doi.org/10.1039/c3mt00347g

KUMARI, M., RAJAK, S., SINGH, S.P., KUMARI, S. I., KUMAR, P.U., MURTY, U.S.N., MAHHOOB, M., GROVER, P., and RAHMAN, M.F., 2012. Repeated oral dose toxicity of iron oxide nanoparticles: biochemical and histopathological alterations in different tissues of rats. Journal of Nanoscience and Nanotechnology, 12(3), 2149–2159. https://doi.org/10.1166/jnn.2012.5796

KUMARI, M., RAJAK, S., SINGH, S. P., MURTY, U.S.N., MAHHOOB, M., GROVER, P., and RAHMAN, M.F., 2013. Biochemical alterations induced by acute oral doses of iron oxide nanoparticles in Wistar rats. Drug and Chemical Toxicology, 36(3), 296–305. https://doi.org/10.1166/jnn.2012.5796

LEE, M.J.E., VEISEH, O., BHATTARAI, N., SUN, C., HANSEN, S.J., DITZLER, S., KNOBLAUGH, S., LEE, D., ELLENBOGEN, R., and ZHANG, M., 2010. Rapid pharmacokinetic and biodistribution studies using cholorotoxin-conjugated iron oxide nanoparticles: a novel non-radioactive method. PloS One, 5(3), e9536. https://doi.org/10.1021/nn1008512

LIANG, L., COOK, W.D., and ZHU, J., 2008. DEA models for two-stage processes: Game approach and efficiency decomposition. Naval Research Logistics (NRL), 55(7), 643–653. https://doi.org/10.1002/NAV.20308

LIU, Y., LI, J., XU, K., GU, J., HUANG, L., ZHANG, L., LIU, N., KONG, J., XING, M., and ZHANG, L., 2018. Characterization of superparamagnetic iron oxide nanoparticle-induced apoptosis in PC12 cells and mouse hippocampus and striatum. Toxicology Letters, 292, 151–161.https://doi.org/10.1016/j.toxlet.2018.04.033

LOEFFLER, D.A., CONNOR, J.R., JUNEAU, P.L., SNYDER, B.S., KANALEY, L., DEMAGGIO, A.J., NGUYEN, H., BRICKMAN, C.M., and LEWITT, P.A., 1995. Transferrin and iron in normal, Alzheimer's disease, and Parkinson's disease brain regions. Journal of Neurochemistry, 65(2), 710–716.https://doi.org/10.1046/j.1471-4159.1995.65020710.x

LOTTI, M. 2010. Clinical toxicology of anticholinesterase agents in humans. In Hayes' Handbook of Pesticide

Toxicology pp. 1543-1589. https://doi.org/10.1016/B978-0-12-374367-1.00072-0

LU, M., COHEN, M.H., RIVES, D., and PAZDUR, R., 2010. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. American Journal of Hematology, 85(5), 315–319. https://doi.org/10.1002/ajh.21656

MIURA, N., and SHINOHARA, Y., 2009. Cytotoxic effect and apoptosis induction by silver nanoparticles in HeLa cells. Biochemical and Biophysical Research Communications, 390(3), 733–737. https://doi.org/10.1016/j.bbrc.2009.10.039

MOHAMMAD, F.K., Al-ZUBAIDY, M.H., and ALIAS, S.A. **2007**. Electrometric Determination of Erythrocyte, Plasma and Whole Blood Cholinesterase Activities in Sheep, Goats and Cattle and Their in vitro Inhibition by Anticholinesterase Insecticides. Journal of Pharmacology and Toxicology,2(2),131-141. https://doi.org/10.3923/JPT.2007.131.141

NEL, A., XIA, T., MADLER, L., and LI, N., 2006. Toxic potential of materials at the nanolevel. Science, 311(5761), 622–627. https://doi.org/10.1126/science.1114397

OHKAW, H., OHISI, N., and YAGI, K., 1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Analytical Biochemistry, 95(2), 351–358. https://doi.org/10.1016/0003-2697(79)90738-3

REDDY, U.A., PRABHAKAR, P.V, and MAHBOOB, M., 2017. Biomarkers of oxidative stress for in vivo assessment of toxicological effects of iron oxide nanoparticles. Saudi Journal of Biological Sciences, 24(6), 1172–1180. https://doi.org/10.1016/j.sjbs.2015.09.029

ROMANO, D., BONOMI, F., DE MATTOS, M.C., DE SOUSA, FONSECA, T., DE OLIVEIRA, M.C., and MOLINARI, F., 2015. Esterases as steroselective biocatalysts. Biotechnology Advances 33(5): 547-565. https://doi.org/10.1016/j.biotechadv.2015.01.006

ROUAULT, T.A., and TONG, W.H., 2008. Iron–sulfur cluster biogenesis and human disease. Trends in Genetics, 24(8), 398–407. https://doi.org/10.1016/j.tig.2008.05.008

VOSS, L., HOCHE, E., STOCK, V., BOHMERTHMERT, L., BRAEUNING, A., THUENEMANN, A. F., and SIEG, H., 2021. Intestinal and hepatic effects of iron oxide nanoparticles. Archives of Toxicology, 95, 895–905. https://dx.doi.org/10.1007/s00204-020-02960-7

WANG, B., FENG, W.Y., WANG, M., SHI, J.W., ZHANG, F., OUYANG, H., ZHAO, Y.L., CHAI, Z.F., HUANG, Y.Y., and XIE, Y.N., 2007. Transport of intranasally instilled fine Fe2O3 particles into the brain: micro-distribution, chemical states, and histopathological observation. Biological Trace Element Research, 118(3), 233–243. https://doi.org/10.1007/s11051-007-9245-3

WANG, W., KNOVICH, M.A., COFFMAN, L.G., TORTI, F.M., and TORTI, S.V., 2010. Serum ferritin: past, present and future. Biochimica et Biophysica Acta (BBA)-General Subjects, 1800(8), 760–769. http://dx.doi.org/10.1016/j.bbagen.2010.03.011

YEH, Y.C., CRERAN, B., and ROTELLO, V.M., 2012. Gold nanoparticles: preparation, properties, and applications in bionanotechnology. Nanoscale, 4(6), 1871–1880. http://dx.doi.org/10.1039/c1nr11188d

ZHU, M.T., FENG, W.Y., WANG, Y., WANG, B., WANG, M., OUYANG, H., ZHAO, Y.L., and CHAI, Z.F., 2009. Particokinetics and extrapulmonary translocation of intratracheally instilled ferric oxide nanoparticles in rats and the potential health risk assessment. Toxicological Sciences, 107(2), 342–351. https://doi.org/10.1093/toxsci/kfn245

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