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Hepatotoxicity Induced by Some Metal Nanoparticles *In Vivo*: Review

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Abstract

Nanotechnology has witnessed a revolution in our current era and has penetrating into consumer industries, biomedical and electronic fields, and environmental treatments, due to the chemical-physical properties of nanoparticles, especially metal ones, and the advantage of large surface area to volume. Thus, the growing consumption of these minutes has increased the exposure of living organisms to potential risks associated with their toxicity, especially vital organs as liver. The present review summarizes the potential hepatotoxicity in vivo (rat model) of experimentally exposed metal nanoparticles or their oxides. Most of the literature indicates that the induced hepatotoxicity is due to oxidative stress, cytotoxicity, and disturbance of liver function depending on the concentrations and method of exposure to these nanoparticles. Therefore, the toxic potential must be taken into account and the damage that may be caused to other vital organs in the body must be constantly evaluated in order to reach safe use of these nanoparticles.

Keywords: *Nanotechnology, environmental treatments, hepatotoxicity, cytotoxicity.*

Introduction

Nanoparticles (NPs) are engineered materials with a size range of 1-100 nm [1]. These particles have been exploited with unparalleled merit in various biotechnology and medical applications [2,3] due to their small size and larger surface area to volume ratio [4], in addition to their unique physical, chemical and electrical properties [5]. NPs are used in many consumer products, as paints and ceramics [6], as well as in cosmetics, which has become popular in the current era [7], in addition to being recruited as a new delivery system for drugs [8], biosensors [9], and cancer treatment [10]. The growing application of MNPs has led to an increasing release of these materials into the environment, threatening human life and other living organisms. Therefore, its potential toxicity to environmental health has received more attention [11]. It is worth noting that NPs are considered more toxic to the living body compared to large particles of the same chemical substance [12]. In this regard, many experimental studies have been conducted to evaluate the toxicity related to NPs, with the aim of reaching the safe use of these particles [13-15]. MNPs can penetrate the body in possible ways, such as inhalation, orally, or through the skin, and accumulate in vital organs of the body [16], including the liver, kidneys, heart, lungs, and brain, in addition to the spleen and digestive system, via the blood or lymphatic system [16-18]. These particles can also easily cross cell membranes and cause cytotoxicity [19]. Many recent experimental nanoparticle toxicology studies have confirmed that MNPs accumulate in higher quantities in liver than in rest of body, inducing structural and functional damage to hepatocytes [20-22]. From the above, this article aims to review the hepatotoxicity induced by metal nanoparticles or their oxides in vivo, especially the rat model.

Nanoparticles and their induced liver toxicity

Silver Nanoparticles

Silver nanoparticles (AgNPs) remain distinct among

MNPs to date due to their many commercial uses [23], as more than 300 tons of these nanoparticles are manufactured annually and are recruited in biomedical applications, household appliances and food product storage [24]. They are characterized by their antimicrobial, optical, electrical and catalytic properties [25,26]. In a study conducted by Yousef *et al*. (2022), they administered intraperitoneal injections of AgNPs as spherical forms with sizes ranging from (7.7 - 28.4 nm) to adult male rats (low dose, 1 mg/kg, and high dose, 2 mg/kg), daily for 30 days. They found that AgNPs caused significant damage to liver tissue, characterized by elevated levels of liver function indicators, oxidative stress, and inflammatory markers TNF-α and IL-6, with a significant decrease in total protein, total albumin, and antioxidants in hepatic tissue. This was accompanied by marked histopathological changes through the destruction of normal hepatic architecture, with a decrease in the numbers of normal liver cells versus an increase in necrotic liver cells and inflammatory cells, leading to hepatotoxicity [27]. Parang and Moghadamnia (2018) in their experiment on adult male Wistar rats injected with silver nanoparticles intraperitoneally with doses of 25 and 100 mg/kg for 14 days respectively observed enhanced serum levels of hepatic enzymes and increased liver tissue necrosis as well [28]. Shehata et al. (2022) confirmed that Ag-NPs (50 nm) have hepatotoxic and nephrotoxic effects in Sprague-Dawley rats via various mechanisms including oxidative stress, inflammation, and apoptosis [29]. In another experimental study by Ramadhan and Ghareeb (2021), male rats were treated with 50 µl/kg/day of AgNPs for 28 continuous days. The toxic effect of silver nanoparticles (AgNPs) on liver function parameters was confirmed [30].

Gold Nanoparticles

Gold nanoparticles (AuNPs) have gained immense importance due to their catalytic, electronic, fluorescence and biological potential [31,32]. These nanoparticles applied widely in biomedical felid as diagnosis many diseases, drug delivery, and cancers medications [33]. There are many studies that have proven negative functional and even structural changes induced by these nanoparticles in various vital organs including liver at high concentrations[34-36]. In a study by Abdelhalim et al. (2018), they found that administering a dose of 50 µl of 10 nm gold nanoparticles intraperitoneally for 7 days resulted in inflammatory liver damage through an increase in the serum levels of alkaline phosphatase, total protein, alanine aminotransferase, total bilirubin, besides malondialdehyde in hepatic tissue and low glutathione levels in adult rats [37]. In a study by Jarrar et al. (2022), they found that exposing healthy male Wistar Albino rats to 20 injections of 10 nm gold nanoparticles at a daily dose of 2 mg/kg induced hepatic changes including hepatocyte degeneration, cytoplasmic vacuolization, and nuclear modifications with sinusoidal expansion [38]. In another previous study, adult male rats received gold NPs at a dose of 1100 µg/kg orally for 42 days, and the rats showed a significant increase ($P<0.05$) in serum liver enzyme levels indicating a considerable effect on liver function disorders [39].

Zinc oxide Nanoparticles

They are metal oxide nanoparticles (ZnONPs) with wide uses in industry, biomedicine, and cosmetics [40]. These particles have unique antibacterial and antitumor properties, high catalytic as well as high photochemical activities [41]. However, there are reports indicating their potential toxicity to the living body, such as hepatotoxicity, nephrotoxicity, and neurotoxicity [42-44]. Aboulhoda et al. (2020), confirmed in their experiment on rats that exposure to zinc oxide NPs led to histological and functional liver changes. This hepatotoxicity was due to oxidative stress-induced apoptosis coupled with induction of JNK/p38MAPK and STAT-3 signaling [45]. A previous experiment was conducted to estimate pathological effects of ZnONPs on liver by dosing adult rats with 50 mg/kg of ZnONPs for 28 days. The results confirmed a significant increase in the activity of serum liver enzymes resulting from liver dysfunction [46]. In a study by Sakr and Steenkamp (2021), albino male rats were exposed to zinc oxide nanoparticles (200 mg/kg) for 30 days. They noted that sub-chronic exposure caused toxicity, oxidative stress, and hereditary disorders in the liver and thyroid gland [47]. On the other hand, it has been demonstrated by Hosseini et al (2020) have proven that zinc oxide nanoparticles at high doses for 30 days twice a week have toxic effects on liver and pancreas, as they recorded tissue destruction and cellular changes in adult female rats [48]. According to the results of rat model experiment by Ramadan et al., liver cells could exhibit genotoxicity and cytotoxicity after being exposed to zinc oxide NPs with sizes of 30 nm for ten weeks [49].

Copper oxide nanoparticles

Copper oxide nanoparticles (CuONPs) are widely employed in many industrial applications, electronics and environmental treatments, as well as an antibacterial and antifungal agent due to their distinct

elastic and electrochemical properties [50,51]. The seriousness of its environmental pollution has received special attention from many environmental scientists [52-55]. There are many literatures that have confirmed that CuONPs in vivo provoke the generation of reactive oxygen species, oxidative stress, and cytotoxicity and hepatotoxicity [56-58]. In a recent study by Haroun *et al.* (2023), they concluded that treatment of rats orally with CuONPs (20-30 nm) at 100 mg/kg for continuous 8 weeks led to bioaccumulation of copper in the liver and damage through increased serum ALT activity, decreased hepatic arginase activity, and serum total protein content along with increased oxidative stress (lipid peroxidation), inflammation, and apoptosis. It also resulted in severe DNA fragmentation as assessed by the comet assay and significant pathological changes in liver architecture [59]. In a study by Ghonimi and colleagues (2022), they injected healthy mature rats intraperitoneally with CuONPs at different doses for 9 consecutive days. They observed that increasing the dose of these NPs induced hepatotoxicity through severe necrosis of hepatocytes with complete disruption of hepatic rays and loss of hepatic structures [60].

Conclusion

It is necessary to make the use of nanoparticles and their release to the environment as well as living organisms as safe as possible and thus reduce their potential toxicity to the living body. Also pay attention to applying sustainable standards in various fields regarding the environment to ensure the regulation of pollution and the prevention of toxins harmful to public health.

References

1. Ghareeb, O. A. (2023). Hematotoxicity Induced by Copper Oxide Nanoparticles and the Attenuating Role of Giloy In Vivo. Cureus, 15(10).
2. Zeng, L., Gowda, B. J., Ahmed, M. G., Abourehab, M. A., Chen, Z. S., Zhang, C., ... & Kesharwani, P. (2023). Advancements in nanoparticle-based treatment approaches for skin cancer therapy. Molecular Cancer, 22(1), 10.
3. Kumar, K. (2023). Synthesis of silica oxide nanoparticles and their medical applications. In Oxides for Medical Applications (pp. 79-105). Woodhead Publishing.
4. Taher, G. N., & Ghareeb, O. A. (2022). Adverse effects of iron oxide nanoparticles on some biochemical markers and ameliorative effect of Silymarin. Biochemical and Cellular Archives, 22(1), 1829-1832.
5. Suryawanshi, S. M., Badwaik, D. S., Shinde, B. S., Gaikwad, K. D., Shkir, M., Chandekar, K. V., & Gundale, S. (2023). A comprehensive study on structural, magnetic and dielectric properties of Ni0. 3Cu0. 3Zn0. 4Fe1. 8Cr0. 2O4 nanoparticles synthesized by sol-gel auto combustion route. Journal of Molecular Structure, 1272, 134173.
6. Frunză, M., Birsan, A., & Desyatnik, A. (2023). The study of the interaction of tisio4 nanoparticles with the model system Allium cepa l. In Natural sciences in the dialogue of generations (pp. 41-41).
7. Mascarenhas-Melo, F., Mathur, A., Murugappan, S., Sharma, A., Tanwar, K., Dua, K., ... & Paiva-Santos, A. C. (2023). Inorganic nanoparticles in dermopharmaceutical and cosmetic products: Properties, formulation development, toxicity, and regulatory issues. European Journal of Pharmaceutics and Biopharmaceutics, 192, 25-40.
8. Liu, R., Luo, C., Pang, Z., Zhang, J., Ruan, S., Wu, M., ... & Gao, H. (2023). Advances of nanoparticles as drug delivery systems for disease diagnosis and treatment. Chinese chemical letters, 34(2), 107518.
9. Siciliano, G., Alsadig, A., Chiriacò, M. S., Turco, A., Foscarini, A., Ferrara, F., ... & Primiceri, E. (2023). Beyond traditional biosensors: Recent advances in gold nanoparticles modified electrodes for biosensing applications. Talanta, 125280.
10. Ahmed, F. F., Ghareeb, O. A., & Al-Bayti, A. A. H. (2022). Nephro Defensive Efficiency of Cichorium Intybus Against Toxicity Caused by Copper Oxide Nanoparticles. Pakistan Journal of Medical & Health Sciences, 16(03), 542-542.
11. García-Mayagoitia, S., Torres-Gómez, A. P., Pérez-Hernández, H., Patra, J. K., & Fernández-Luqueño, F. (2023). Collateral effects of nanopollution on human and environmental health. In Agricultural and Environmental Nanotechnology: Novel Technologies and their Ecological Impact (pp. 619-645). Singapore: Springer Nature Singapore.
12. Sukhanova, A., Bozrova, S., Sokolov, P., Berestovoy, M., Karaulov, A., & Nabiev, I. (2018). Dependence of nanoparticle toxicity on their physical and chemical properties. Nanoscale research letters, 13, 1-21.

13. Długosz, O., Szostak, K., Staroń, A., Pulit-Prociak, J., & Banach, M. (2020). Methods for reducing the toxicity of metal and metal oxide NPs as biomedicine. Materials, 13(2), 279.
14. Ghareeb, O. A. (2023). Adverse Impact of Titanium Dioxide Nanoparticles on Hepato-Renal Functions and Improved Role of Rosmarinus Officinalis. Journal of Natural Science, Biology and Medicine, 14(1), 34.
15. Ajdary, M., Moosavi, M. A., Rahmati, M., Falahati, M., Mahboubi, M., Mandegary, A., ... & Varma, R. S. (2018). Health concerns of various nanoparticles: A review of their in vitro and in vivo toxicity. Nanomaterials, 8(9), 634.
16. Ghareeb, O. A., & Ali, Q. A. (2023). Pathotoxic Impact of Zinc Oxide Nanoparticles on Liver Function and Protective Role of Silymarin. Current Innovations in Disease and Health Research, 3, 153-161.
17. Wu, T., & Tang, M. (2018). Review of the effects of manufactured nanoparticles on mammalian target organs. Journal of Applied Toxicology, 38(1), 25-40.
18. Chrishtop, V. V., Mironov, V. A., Prilepskii, A. Y., Nikonorova, V. G., & Vinogradov, V. V. (2021). Organ-specific toxicity of magnetic iron oxide-based nanoparticles. Nanotoxicology, 15(2), 167-204.
19. Liu, N., & Tang, M. (2020). Toxic effects and involved molecular pathways of nanoparticles on cells and subcellular organelles. Journal of Applied Toxicology, 40(1), 16-36.
20. Ghareeb, O. A. (2023). Destructive Effect of Nickel Oxide Nanoparticles on Some Liver and kidney Indices and Ameliorative Role of Thyme Oil. IAR J. Med Sci, 4(6), 6-12.
21. Yan, N., Wang, Y., Wong, T. Y., Hu, Y., Xu, H., Alessandro, P., ... & Shi, J. (2023). Surface topography of nanoplastics modulates their internalization and toxicity in liver cells. Environmental Science: Nano, 10(10), 2685-2700.
22. Babaei, A. A., Rafiee, M., Khodagholi, F., Ahmadpour, E., & Amereh, F. (2022). Nanoplastics-induced oxidative stress, antioxidant defense, and physiological response in exposed Wistar albino rats. Environmental Science and Pollution Research, 1-13.
23. Ghareeb, O. A., Sulaiman, R. R., & Ibrahim, S. H. (2021). Impact of silver nanoparticles on hematological profiles and hepatorenal functions in photosensitivity: In Vivo. Annals of the Romanian Society for Cell Biology, 7448-7459.
24. Ferdous, Z., & Nemmar, A. (2020). Health impact of silver nanoparticles: a review of the biodistribution and toxicity following various routes of exposure. International journal of molecular sciences, 21(7), 2375.
25. Ghareeb, O. A. (2021). Toxic Effect of Silver Nanoparticles on Some Hematological Parameters and Possible Preventive Role of Moringa Oleifera: In Vivo. Annals of the Romanian Society for Cell Biology, 13796-13801.
26. Pryshchepa, O., Pomastowski, P., & Buszewski, B. (2020). Silver nanoparticles: Synthesis, investigation techniques, and properties. Advances in Colloid and Interface Science, 284, 102246.
27. Yousef, H. N., Ibraheim, S. S., Ramadan, R. A., & Aboelwafa, H. R. (2022). The ameliorative role of eugenol against silver nanoparticles-induced hepatotoxicity in male Wistar rats. Oxidative Medicine and Cellular Longevity, 2022.
28. Parang, Z., & Moghadamnia, D. (2018). Effects of silver nanoparticles on the functional tests of liver and its histological changes in adult male rats. Nanomedicine Research Journal, 3(3), 146-153.
29. Shehata, A. M., Salem, F. M., El-Saied, E. M., Abd El-Rahman, S. S., Mahmoud, M. Y., & Noshy, P. A. (2022). Evaluation of the ameliorative effect of zinc nanoparticles against silver nanoparticle–induced toxicity in liver and kidney of rats. Biological trace element research, 1-11.
30. Ramadhan, S. A., & Ghareeb, O. A. (2021). Toxicity of AgNPs upon liver function and positive role of Tinospora cordifolia: In Vivo. Pak. J. Med. Health Sci, 15(6), 2164-2166.
31. Hammami, I., & Alabdallah, N. M. (2021). Gold nanoparticles: Synthesis properties and applications. Journal of king Saud university-science, 33(7), 101560.
32. Ramadhan, S. A., & Ghareeb, O. A. (2021). Clinicohematological Study of Gold Nanoparticles Toxicity and Ameliorative Effect of Allium Sativum. Annals of the Romanian Society for Cell Biology, 597-602.
33. Siddique, S., & Chow, J. C. (2020). Gold nanoparticles for drug delivery and cancer therapy. Applied Sciences, 10(11), 3824.
34. Ghareeb OA. Hepato-Renal dysfunctions

induced by Gold nanoparticles and preservative efficacy of black seed oil. Journal of Medicinal and Chemical Sciences. 2022;5(1):137-43.
35. Sani, A., Cao, C., & Cui, D. (2021). Toxicity of gold nanoparticles (AuNPs): A review. Biochemistry and biophysics reports, 26, 100991.
36. Fadia, B. S., Mokhtari-Soulimane, N., Meriem, B., Wacila, N., Zouleykha, B., Karima, R., ... & Thorat, N. D. (2022). Histological injury to rat brain, liver, and kidneys by gold nanoparticles is dose-dependent. ACS omega, 7(24), 20656-20665.
37. Abdelhalim, M. A. K., Moussa, S. A. A., Qaid, H. A., & Al-Ayed, M. S. (2018). Potential effects of different natural antioxidants on inflammatory damage and oxidative-mediated hepatotoxicity induced by gold nanoparticles. International Journal of Nanomedicine, 7931-7938.
38. Jarrar, Q., Al-Doaiss, A., Jarrar, B. M., & Alshehri, M. (2022). On the toxicity of gold nanoparticles: Histological, histochemical and ultrastructural alterations. Toxicology and Industrial Health, 38(12), 789-800.
39. Ghareeb, O. A. (2021). Pathological Changes in Liver Function Induced by Gold Nanoparticles and Protective Role of Tinospora Cordifolia: In Vivo. Annals of the Romanian Society for Cell Biology, 660-665.
40. Youssef FS, Ismail SH, Fouad OA, Mohamed GG. Green synthesis and Biomedical Applications of Zinc Oxide Nanoparticles. Review. Egyptian Journal of Veterinary Sciences. 2024 Jan 1;55(1):287-311.
41. Mahmoud JH, Ghareeb OA, Mahmood YH. The role of garlic oil in improving disturbances in blood parameters caused by zinc oxide nanoparticles. Journal of Medicinal and Chemical Sciences. 2022;5(1):76-81.
42. Ramadhan, S. A., & Ghareeb, O. A. (2022). Efficiency of Cichorium Intybus in Reducing Hepatotoxicity Induced by Zinc Oxide Nanoparticles. Annals of Medical and Health Sciences Research| Volume, 12(3).
43. Ghareeb, O. A. (2022). Defense Effect of Ganoderma lucidum Against Zinc Oxide Nanoparticles Induced Nephrotoxicity. Eurasian Medical Research Periodical, 8, 26-34.
44. Eleiwa, N. Z., Ali, M. A. A., Said, E. N., Metwally, M. M., & Abd-ElHakim, Y. M. (2023). Bee venom (Apis mellifera L.) rescues zinc oxide nanoparticles induced neurobehavioral and neurotoxic impact via controlling neurofilament and GAP-43 in rat brain. Environmental Science and Pollution Research, 30(38), 88685-88703.
45. Aboulhoda, B. E., Abdeltawab, D. A., Rashed, L. A., Abd Alla, M. F., & Yassa, H. D. (2020). Hepatotoxic Effect of Oral Zinc Oxide Nanoparticles and the Ameliorating Role of Selenium in Rats: A histological, immunohistochemical and molecular study. Tissue and Cell, 67, 101441.
46. Ghareeb, O. A. (2021). Toxicopathological effects of zinc oxide nanoparticles on the liver function and preventive role of silymarin in vivo. Indian Journal of Forensic Medicine & Toxicology, 15(2), 3212-3217.
47. Sakr S, Steenkamp V. Zinc oxide nanoparticles induce oxidative stress and histopathological toxicity in the thyroid gland and liver of rats. Toxicological & Environmental Chemistry. 2021 Apr 21;103(4):399-422.
48. Hosseini, S. M., Amani, R., Moshrefi, A. H., Razavimehr, S. V., Aghajanikhah, M. H., & Sokouti, Z. (2020). Chronic zinc oxide nanoparticles exposure produces hepatic and pancreatic impairment in female rats. Iranian Journal of Toxicology, 14(3), 145-154.
49. Ramadan, A. G., Yassein, A. A., Eissa, E. A., Mahmoud, M. S., & Hassan, G. M. (2022). Biochemical and histopathological alterations induced by subchronic exposure to zinc oxide nanoparticle in male rats and assessment of its genotoxicicty. Journal of Umm Al-Qura University for Applied Sciences, 8(1-2), 41-49.
50. Akintelu, S. A., Folorunso, A. S., Folorunso, F. A., & Oyebamiji, A. K. (2020). Green synthesis of copper oxide nanoparticles for biomedical application and environmental remediation. Heliyon, 6(7).
51. Alhares, H. S., Ali, Q. A., Shaban, M. A. A., M-Ridha, M. J., Bohan, H. R., Mohammed, S. J., ... & Hasan, H. A. (2023). Rice husk coated with copper oxide nanoparticles for 17α-ethinylestradiol removal from an aqueous solution: adsorption mechanisms and kinetics. Environmental monitoring and assessment, 195(9), 1078.
52. Ali, Q. A., Shaban, M. A. A., Mohammed, S. J., Abd-Almohi, H. H., Abed, K. M., Salleh, M. Z. M., & Hasan, H. A. (2023). Date Palm Fibre Waste Exploitation for the Adsorption of Congo Red Dye via Batch and Continuous Modes. Journal of Ecological Engineering, 24(10).
53. Ali, Q. A., & Ghareeb, O. A. (2023). Achieving Sustainable Development Goals by Wastewater

Management. Zeta Repository, 19, 99-108.
54. Ali QA, Ghareeb OA. Drinking Water Quality and Its Impact on Public Health. Web of Scientist: International Scientific Research Journal. 2023 Sep;4(9):48-64.
55. Salman, M. S., Alhares, H. S., Ali, Q. A., M-Ridha, M. J., Mohammed, S. J., & Abed, K. M. (2022). Cladophora algae modified with CuO nanoparticles for tetracycline removal from aqueous solutions. Water, Air, & Soil Pollution, 233(8), 321.
56. Ghareeb, O. A., Mahmoud, J. H., & Qader, H. S. (2021). Efficacy of Ganoderma lucidum in reducing liver dysfunction induced by copper oxide nanoparticles. Journal of Research in Medical and Dental Science, 9(12), 14-17.
57. Anreddy, R. N. R. (2018). Copper oxide nanoparticles induces oxidative stress and liver toxicity in rats following oral exposure. Toxicology Reports, 5, 903-904.
58. Ghareeb OA, Ramadhan SA. Prophylactic Efficacy of Silymarin upon Renal Dysfunction Induced by Copper Oxide Nanoparticle. Journal Healthcare Treatment Development. 2023 Oct;3(06):29-38.
59. Haroun, A. M., El-Sayed, W. M., & Hassan, R. E. (2023). Quercetin and L-Arginine Ameliorated the Deleterious Effects of Copper Oxide Nanoparticles on the Liver of Mice Through Anti-inflammatory and Anti-apoptotic Pathways. Biological Trace Element Research, 1-13.
60. Ghonimi, W. A., Alferah, M. A., Dahran, N., & El-Shetry, E. S. (2022). Hepatic and renal toxicity following the injection of copper oxide nanoparticles (CuO NPs) in mature male Westar rats: histochemical and caspase 3 immunohistochemical reactivities. Environmental Science and Pollution Research, 29(54), 81923-81937.