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Research Article

HEPATOTOXICITY OF COPPER OXIDE NANOPARTICLES (CuONPs) IN WESTAR RATS

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ABSTRACT

The use of nanoparticles in human activities has increased. Therefore, study of the biological effects of different nanoparticles and nanocomposite materials, specially their effects on human and animal organs need special attention. The primary concern is the toxicity of nanoparticles in humans and the potential risk of nanoparticles and their related products on human health. Copper nanoparticles are widely synthesized and used as metal catalyst, heat transfer fluids in machine tools, semiconductors, and even in antibacterial medications, etc. The present investigation was carried out on forty apparently healthy mature westar rats weighing between 120-200 gm with average three months age. The rats were obtained from laboratory animal unite in the faculty of pharmacy, King Saud University and were divided randomly into four groups (10 rats/ group). Group I (G1) was kept as a control and fed with a basal diet without CuO NPs for 9 days. Group II (G2)was obtained CuO NPsin a dose 5 mg/ kg body weight, Group III(G3)was obtained CuO NPsin a dose 10 mg/ kg body weight and Group IV(G4)was obtained CuO NPsin a dose 25 mg/ kg body weight. All treated groups obtained CuO NPs by intraperitonealinjection for 9 days. At the end of experiment, cervical dislocation of rats and the livers were taken for the histological studies. The histopathologicalfinding of G1 revealed normal histological structure of all hepatic tissues without any abnormalities. Meanwhile, G2 and G3 clarified mild to moderate necrosis of the hepatocytes, disorganization of the hepatic cords, microvesicularsteatosis, moderate sinusoidal dilatation with congestion and inflammatory cells infiltration with fibrous tissue proliferation. With Prussian blue reaction, the G2 was observed devoid of any hemosiderin pigments precipitation within the hepatocytes but G3 clarified moderate hemosiderin pigments precipitation. On the other hand, liver of G4 showed sever necrosis of the hepatic parenchyma with loss of all hepatic architectures, inter hepatocellular bleeding, severe steatosis, sever sinusoidal dilatation with congestion accompanied by Kupffer cells hyperplasia and sever lymphocytes aggregation within the hepatic parenchyma. With Prussian blue reaction, sever hemosiderin pigments precipitation within the hepatic tissue was recognized. The present investigation was concluded that the CuO NPs have potential oxidative stress in the hepatic tissues that may affect the function of the liver.

INTRODUCTION

Nanomaterials have gained increasing attention because of their novel properties, including a large specific surface area and high reaction activity (Yan *et al.,* 2012 and Amelia *et al.,* 2012). Due to rapid development of nanotechnology, nanomaterials with various shapes and diameters have been prepared and used in some industrial products and commodities (Joh *et al.,* 2011, Tang *et al.*, 2012 and Laurent *et al.,* 2008).

Metal oxide nanoparticles (NPs) belong to a family of nanomaterials that have been manufactured on a large scale for both industrial and household applications, and they hold promise for future applications (Chang *et al*., 2012).

Copper oxide nanoparticles (CuO NPs) are used in a number of technical applications such as catalysts, wood protection, electronics, and antimicrobial products (Ahamed *et al.,*2014, Ben-Moshe *et al.,*2009, Bhaumik *et al.,* 2014, Evans *et al.,*2008 and Ren *et al.,* 2009). They are also used as additives in inks (Zenou *et al.,* 2014) and coatings in food packaging (Longano *et al.,* 2012). Furthermore, CuONPs have strong superconductive properties so they are included in many different consumer electronics including gas sensors, batteries, and solar cells (Bondarenko *et al*., 2013). Moreover, nano-

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copper particles are used as the additive in lubricants, polymers/plastics, metallic coating, etc. Due to excellent mending effects of nano-copper particles, they are added into lubricant oil as an additive to effectively reduce friction and wear, or to mend a worn surface (Liu *et al.,* 2004). Nano-copper particles are homogeneously deposited on the surface of graphite to improve the charge-discharge property significantly, such as coulombic efficiency, cycle characteristics, and high rate performance as an anode material for lithium ion batteries. Researchers have thought that CuO-NPs were highly toxic when compared with other metal oxide nanoparticles as well as bulk Cu (Karlsson *et al.,* 2008 and Heinlaan *et al.,* 2008)

Cu-NPs are also used as one of the main constituents of fungicides, algaecide and herbicides however they can cause genotoxicity and oxidative DNA damage at cellular level (Song *et al*., 2012). Cu-NPs have the ability to cross the plasma membrane, cause oxidative stress via interacting with subcellular organelles (Fahmy & Cormier, 2009; Melegari *et al*., 2013; Wang *et al*., 2011 and Gómez *et al*., 1998) and can accumulate in the tissues such as liver and gills of fish (Wang *et al*., 2013 and Griffitt *et al*., 2007).

Recently, the use of nanoparticles in human activities has increased. Therefore, study of the biological effects of different nanoparticles and nanocomposite materials, specially their effects on human and animal organs need special attention. The primary concern is the toxicity of nanoparticles in humans and the potential risk of nanoparticles and their related products on human health. Copper nanoparticles are widely synthesized and used as metal catalyst, heat transfer fluids in machine tools, semiconductors, and even in antibacterial medications (Aruoja *et al.,* 2009 and Wang *et al.,* 2004).

Aim of work

The present investigation wasperformed to clarify and evaluate the hepatotoxicity of copper oxide nanoparticles (CuONPs) ofWestarrats.

MATERIALS AND METHODS

Animals and housing

Forty apparently healthy mature Westar rats weighing between 120-200 gm with average three months age wereobtained from laboratory animal unite in the faculty of pharmacy, King Saud University. The rats were randomly divided into four groups and kept in galvanized standard cages, ten animals/cage, under hygienic conditions and left for one week before starting the experiment for accommodation. Feed and water were available ad libitum.Temperature was recorded continuously, and maintained between (20 and 23 °C) along the experimental period. A cycle of 14 h of light and 10 h of dark was fixed throughout the experiment. All animals were handled and all experiments were conducted in accordance with the protocols approved by King Saud University Animal Care Ethical Committee while the experimental procedures were carried out in accordance with international guidelines for care and use of laboratory animals.

Supplements (Nanoparticles)

Well-dispersed CuO NPs (nanopowder<50 nm particle size) at 50 wt% in distilled water (Sigma, Aldrich) were used in the present study. The nanoparticles dispersion had the following characterization: concentration 50 wt.% in H2O; pH 5.5 ± 0.1; density 1.7 g/ml ± 0.1 g/ml, crystalline shape, diameter <50 nm, length <50 nm and surface area 29 m2/g.

Experimental design

Forty rats were divided randomly into four groups (10 rats/ group) and subjected for 9 days to one of the following treatments:

Group I(G1) kept as a control and fed with a basal diet without CuO NPs injection for 9 days.
Group II (G2)was obtained CuO NPsin a dose 5 mg/ kg body weight/day by intraperitonealinjectionfor 9 days.
Group III(G3)was obtained CuO NPsin a dose 10 mg/ kg body weight/day by intraperitonealinjection for 9 days.
Group IV(G4)was obtained CuO NPsin a dose 25 mg/ kg body weight/day by intraperitonealinjection for 9 days.

Histological and histochemical processing

At the end of experiment, cervical dislocation of rats and for histologicalstudies, liverswere separated and small pieces from them were taken, fixed in neutral buffered formalin10 %, dehydrated, cleared and paraffin ionized for paraffin blocks and 5 micron sections were obtained, mounted on a glass slides and stained with Hematoxylin and Eosin (H&E), and Prussian blue reaction according to Bancroft and Gamble (2001).

RESULTS

The histological examination of the liver in the control group (G1) revealed normalhepatic architecture without any pathological changes. The hepatic parenchyma of this group was observed very homogenous, intact and consisting of numerous hepatic lobules that were difficult demarcated from each other's by a very thin connective tissue trabeculae in between (Plate, 1: Fig. A).

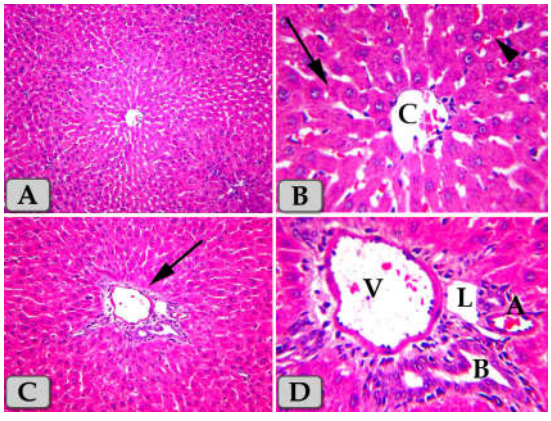

Plate 1 Sections of *male Westar rats* liver of control group (**G1**);
Figure (A): showing normal, intact hepatic parenchyma. H&E Obj.x10: Oc.x10
(B): Higher magnification of fig. A showing regular radiated hepatic cords (arrow) from the central vein (C), intact sinusoids (arrow head). H&E Obj.x40 : Oc.x10
(C): showing normal portal triad. H&E Obj.x10 : Oc.x10
(D): Higher magnification of fig. C showing intact portal vein (V), hepatic artery (A), lymph vessel (L) and bile ductules (B). H&E Obj.x40 : Oc.x10

Furthermore, the hepatic lobule was appeared bounded centrally with central vein and peripherally with portal triad. The major compartment of each hepatic lobule were the hepatocytes and appeared irregular polygonal or polyhedral shaped cells typically with single, central, large vesicular

nucleus with fine dispersed chromatins in most cases, however, some of them appeared occasionally bi-nucleated(Plate, 1: Fig. B). In addition, hepatocytes were dorsally radiating from the central vein towards the periphery; portal triad forming the hepatic cords. Moreover, the hepatic sinusoids were observed distributing in between the hepatic cords supplying the hepatocytes with normal, intact lining epithelium (Plate, 1: Fig. B). Each hepatic lobule was bounded peripherally with portal triad that housingbranches from portal vein, hepatic artery, lymph vesseland bile ductules (Plate, 1: Fig. C and D).

Meanwhile, G2 treated with CuO NPs in a dose of 5 mg/kg. bwt and G3 treated with CuO NPs in a dose of 10 mg/kg. bwtclarified mild to moderate necrosis of the hepatocytes with moderate degeneration and disorganization of the hepatic cords (Plate, 2: Fig. A and B).

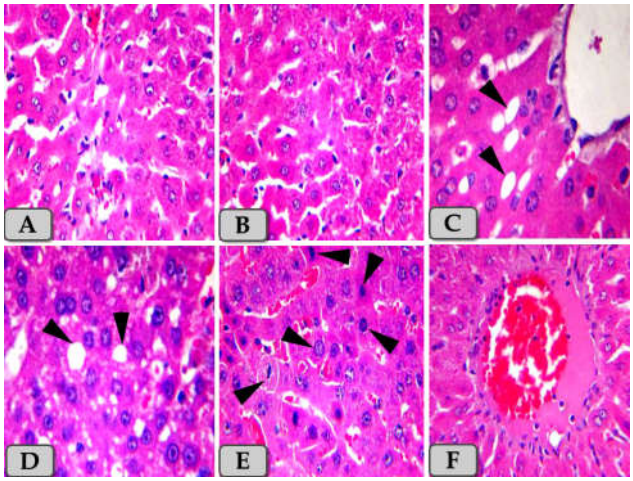

Plate 2 Sections of *male Westar rats*liver of G2 treated with CuO NPs in dose of 5 mg/kg. bwt and G3 treated with CuO NPs in a dose of 10 mg/kg bwt by intraperitonealinjection for 9 days

(A and B): showing moderate necrosis of the hepatic parenchyma and disorganization of the hepatic cords. A and B)H&E Obj.x40 : Oc.x10
(C and D): showing moderate microvesicularsteatosis in hepatocytes cytoplasm (arrow head).C and D)H&E Obj.x40 : Oc.x10
(E): showinghepatocytes withpoleomorphic nuclei and with different size & activity (arrow head). H&E Obj.x40 : Oc.x10
(F): showing moderate congestion within the central vein. H&E Obj.x40 : Oc.x10

And also, microvesicularsteatosis was observed within the hepatocytes cytoplasm (Plate, 2: Fig. C and D). Many hepatocytes possessed poleomorphic nuclei with different size and different activity where some nuclei observed with euchromatic and other with heterochromatic chromatin (Plate, 2: Fig. E).And also, moderate congestion within the central vein (Plate, 2: Fig. F) and also in the portal vein in the portal triadwas observed (Plate, 3: Fig. G). Furthermore, moderate sinusoidal dilatation with congestion in between the hepatic cords was clarified (Plate, 3: Fig. H). In addition, focal scattered of inflammatory cells infiltration with fibrous connective tissue proliferation was demonstrated within the hepatic parenchyma (Plate, 3: Fig. J) and especially in portal areas (Plate, 3: Fig. I). Moderate hyperplasia of the bile duct was also observed (Plate, 3: Fig. K).With Prussian blue reaction, the G2 treated with CuO NPs in a dose of 5 mg/kg was showed devoid of any hemosiderin pigments precipitation within the hepatocyte (Plate, 3: Fig. L). Meanwhile, G3 treated with CuO NPs in a dose of 10 mg/kg clarified moderate hemosiderin pigments precipitation within the hepatocyte (Plate, 3: Fig. M, N and O).

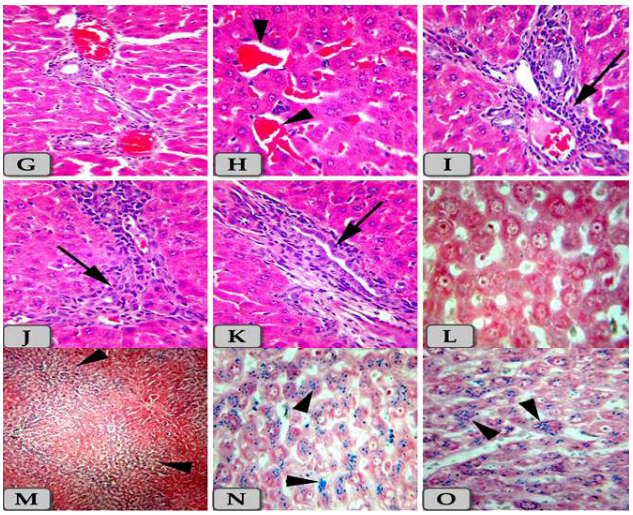

Plate 3 Sections of *male Westar rats*liver of G2 and G3

(G): showing moderate congestion within the portal vein in the portal triad. H&E Obj.x20 : Oc.x10
(H): showingmoderate dilatation and congestion within the hepatic sinusoids (arrow head). H&E Obj.x40: Oc.x10
(I): showing moderate inflammatory cells infiltration with fibrous tissue proliferation within the portal area (arrow). H&E Obj.x40 : Oc.x10
(J): showing moderate inflammatory cells infiltration with fibrous tissue proliferation within the hepatic parenchyma (arrow). H&E Obj.x40: Oc.x10
(k): showing moderate hyperplasia of bile duct(arrow). H&E Obj.x40: Oc.x10
(L):photomicrograph of liver of G2 showing negative Prussian blue reaction of hepatocyte. Prussian blue reactionObj.x40: Oc.x10
(M):photomicrograph of liver of G3 showing moderate positive Prussian blue reaction of hepatic tissue (arrow head). Prussian blue reactionObj.x10 : Oc.x10
(N and O):photomicrograph of liver of G3 showing moderate hemosiderin pigments precipitation within the hepatocytes cytoplasm (arrow head). N and O) Prussian blue reactionObj.x40: Oc.x10

On the other hand, liver of G4 treated with CuO NPs in a dose of 25 mg/kg. bwt showed diffuse degeneration and necrosis of the hepatic tissues with loss of the hepatic architectures. Furthermore, sever disorganization of hepatic cords was claimed.

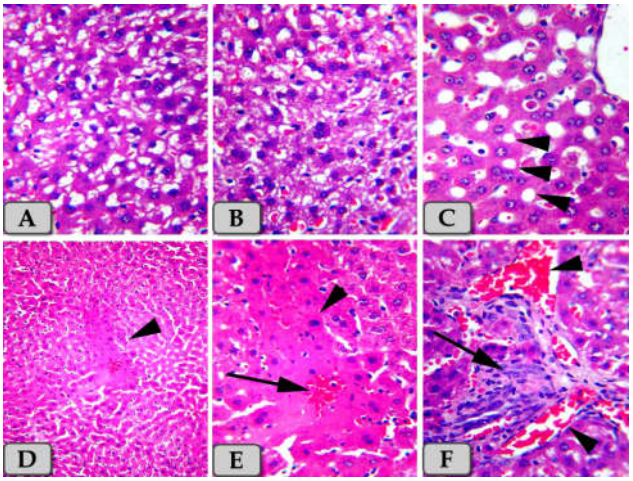

Plate 4 Sections of *male Westar rats*liver of G4 treated with CuO NPs in dose of 25 mg/kg. bwt by intraperitonealinjection for 9 days

(A and B): showing sever disorganization of the hepatic cords, severe necrosis in the hepatocytes with pyknotic cellular nuclei and condensed chromatin. A and B) H&E Obj.x40 : Oc.x10
(C): showing severmicrovesicularsteatosis (arrow head).H&E Obj.x40: Oc.x10
(D and E): showing focal area of hepatocellular necrosis with pyknotic nuclei (arrow head) and hemorrhage in between the hepatocytes (arrow) .D, E)H&E D) Obj.x10 : Oc.x10 E) Obj.x40 : Oc.x10
(F):showingsever sinusoidal dilatation and congestion (arrow head) with inflammatory cell infiltrations (arrow). H&E Obj.x40: Oc.x10

In addition, sever degenerative changes which were evident in numerous hepatocytes; enlarged cells, had light and foamy cytoplasm filled with vacuoles of variable size that were tended to form cystic degeneration were demonstrated. And also, hepatocytes necrotic changes were evident; a small, pyknotic cellular nuclei with condensed chromatin, lack of nucleolus and acidophilic cytoplasmas well as apoptosis were recognized (Plate, 4: Fig. A, B, D and E). In addition, inter hepatocellular bleeding was observed (Plate, 4: E). And also, severe microvesicularsteatosis within the hepatocytes cytoplasm was claimed (Plate, 4: C). Furthermore, sever sinusoidal dilatation with congestion accompanied by Kupffer cells hyperplasia and sever inflammatory cells infiltrations with fibrous tissue proliferation in between the hepatic cords were clarified (Plate, 4: Fig. F and Plate, 5: Fig. G and J). Sever lymphocytes aggregation forming lymphatic nodule like structure or spherical aggregation within the hepatic parenchyma was also noticed (Plate, 5: Fig. H and I). Sever hyperplasia of the bile duct was also observed (Plate, 5: Fig. K and L). Moreover, sever congestion within the portal triad, the portal vein was also demonstrated (Plate, 5: Fig. M). Meanwhile, with Prussian blue reaction, sever hemosiderin pigments precipitation within the hepatic tissue was recognized (Plate, 5: Fig. N and O).

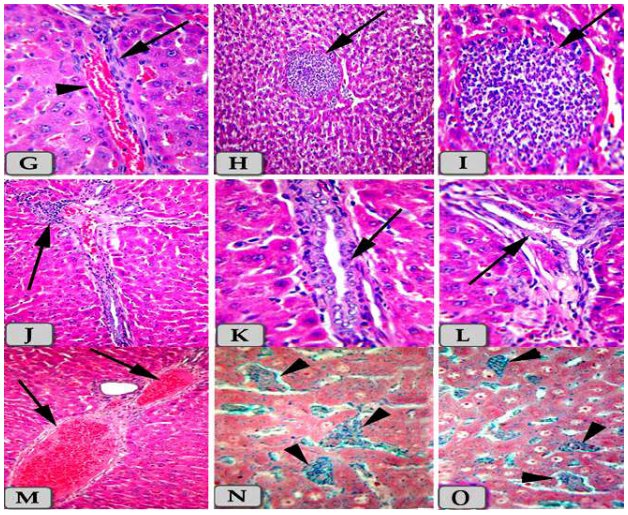

Plate 5 Sections of *male Westar rats*liver of **G4**

(G):showingsever sinusoidal dilatation and congestion (arrow head) with inflammatory cell infiltrations (arrow). H&E Obj.x40 : Oc.x10
(H):showing severlymphocytic aggregation forming nodule or spherical aggregation within the hepatic parenchyma (arrow). H&E Obj.x10 : Oc.x10
(I): Higher magnification of fig. H showingthe lymphocytic aggregation (arrow). H&E Obj.x40 : Oc.x10
(J):showing sever inflammatory cell infiltrations with fibrous tissue proliferation around portal area (arrow). H&E Obj.x10 : Oc.x10
(K and L):showingsever hyperplasia of bile duct (arrow). K, L)H&E Obj.x40 : Oc.x10
(M):showing severcongestion of portal area (arrow). H&E Obj.x10 : Oc.x10
(N and O):showingsever hemosiderin pigments precipitation within the hepatocytes cytoplasm (arrow head). N and O) Prussian blue reactionObj.x40 : Oc.x10

DISCUSSIONS

The histological examination of the liver of the control group (G1) revealed normal hepatic architecture without any pathological changes. Meanwhile, G2 treated with CuO NPs in a dose of 5 mg/kg. bwt and G3 treated with CuONPs in a dose of 10 mg/kg. bwt showed the same effects that exhibited mild to moderate necrosis of the hepatocytes with moderate degeneration & disorganization of the hepatic cords, microvesicularsteatosis within the hepatocytes cytoplasm, hepatocytes with poleomorphic nuclei and different activity, moderate congestion within the central vein and also in the portal vein in the portal triad, moderate sinusoidal dilatation with congestion.Such finding is completely goes hand in hand with the description of Gupta (2016) in common carp (*Cyprinuscarpio*) who described that the histological analysis of control liver showed normal hepatocytes with sinusoidal space. The lower dose treated groups showed significant changes with increased sinusoidal space, cells with pyknotic nuclei and presence of cytoplasmic vacuoles indicating early stages of necrosis. And also, this result is in parallelism with Chen *et al*., (2006) in mice who clarified that at a medium dose level of nano-copper particles, the steatosis around venae centrals of hepatic tissue was observed. Furthermore, Doudi and setorki (2014) described that the histology of the hepatic tissues showed vasculature in central veins and portal triad vessels, and the disappearance of hexagonal liver lobules in all three treatment groups receiving different doses of CuONPs. Moreover, Sizova *et al*., (2012) clarified thatin dosage of 2 mg/kg copper nanoparticles, no structural changes in the organism have been identified in the vascular part of the periportal hepatocytes and in the Kupffer cells cytoplasm of the experimental animals liver. However, in periportalhepatocytes, there are signs ofhydropic degeneration, which is not revealed during the study of an organism 7 days after a one-fold introduction of the metal. At a repeated intramuscular introduction of copper one week later nanoparticles are revealed mainly in the vascular part of the periportal hepatocytes. Herewith one day after the second metal introduction signs of hydropic degeneration are revealed in the vascular part of periportal hepatocytes. Oxyphilic Apoptotic Kaunsilmen cells also appear among hepatocytes. As compared to the control rats, vacuolation of the hepatocytes cytoplasm is observed

With increasing dose of CuO NPs, the liver toxicity became more obvious where, the liver of G4 treated with CuO NPs in a dose of 25 mg/kg. bwt showed diffuse degeneration and necrosis of the hepatic tissues with loss of the hepatic architectures. Furthermore, sever disorganization of hepatic cords was claimed. In addition, sever degenerative changes which were evident in numerous hepatocytes; enlarged cells, had light and foamy cytoplasm filled with vacuoles of variable size that were tended to form cystic degeneration were demonstrated. And also, hepatocytes necrotic changes were evident; a small, pyknotic cellular nuclei with condensed chromatin, lack of nucleolus and acidophilic cytoplasm as well as apoptosis were recognized. In addition, inter hepatocellular bleeding was observed. These results are in parallelism with the result of Gupta (2016) in the common carp (*Cyprinuscarpio*) who claimed that the higher dose treatment showed extensive liver damage as revealed by the presence of hepatocytes with pyknotic nucleus and/or cell with dead nucleus, in addition to aggregation of blood cells and damaged blood vessel. As liver is a key organ in the accumulation and excretion of Cu to metabolism in developing fish, tissue proteome analysis was only performed in this tissue.

Moreover, our finding of necrosis were supported by the result of Ibrahim *et al*., (2015) who clarified that the liver of group II treated with 40 mg/kg BW via oral gavage revealed various histopathological alterations characterized by focal area of hepatocellular necrosis infiltrated by mononuclear cells and polyploidy hepatocytes represented by hepatic

cytokaryomegaly, binucleated hepatocytes associated with activation of Kupffer cells and sporadic cell necrosis as well as apoptosis. Portal triad revealed oval cell proliferation, hyperplasia of biliary epithelium, and formation of newly formed bile ductules in addition to periportal sporadic hepatic cell necrosis and apoptosis. In addition, our result is in parallelism with the observation of Griffitt *et al*., (2007) and Al-Bairuty *et al*., (2013) in fish.

The present study illustrated that sever sinusoidal dilatation with congestion accompanied by Kupffer cells hyperplasia were observed. This finding is in agreement with the results of Sizovaetal., (2012)who showed that Kupffer cell activation may serve as indirect indicator of copper's cytotoxic effect, which is known to be associated with apoptosis, at least, for copper NPs. In addition, Ostaszewska *et al*., (2016) clarified thatfish exposed to AgNPs and CuNPs showed similar pathological changes; dilation of sinusoidal space, overfilled blood vessels, and pyknotic nuclei of the liver. Fish exposed to CuNPs only demonstrated hyaline degeneration in the liver

CONCLUSION

From our investigation, we can conclude that the CuO NPs have potential oxidative stress and with increasing dose, they induced hepatotoxicity that may affect the liver function.

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References

1. Yan L, Zheng YB, Zhao F, Li S, Gao X, Xu B, Weiss PS, Zhao Y (2012) Chemistry and physics of a single atomic layer: Strategies and challenges for functionalization of graphene and graphene-based materials. Chem. Soc. Rev. 41: 97-114.
2. Amelia M, Lincheneau C, Silvi S, Credi A(2012) Electrochemical properties of CdSe and CdTe quantum dots. Chem. Soc. Rev. 41: 5728-5743.
3. Joh DY, Kinder J, Herman LH, Ju SY, Segal MA, Johnson JN, ChanGarnet KL, Park J (2011) Single-walled carbon nanotubes as excitonic optical wires. Nat. Nanotechol. 6: 51-56.
4. Tang F, Li L, Chen D (2012)Mesoporous silica nanoparticles: Synthesis, biocompatibility and drug delivery. Adv. Mater. 24: 1504-1534.
5. Laurent S, Forge D, Port M, Roch A, Robic C, van der Elst L, Muller RN (2008) Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem. Rev. 108: 2064-2110.
6. Chang YN, Zhang M, Xia L, *et al*. (2012)The toxic effects and mechanisms of CuO and ZnO nanoparticles. Materials. 5:2850-2871.
7. Ahamed MAH, Alhadlaq HA, Khan MaM, Karuppiah P, Al-Dhabi NA (2014) Synthesis, characterization, and antimicrobial activity of copper oxide nanoparticles. J Nanomaterials2014:1-4.
8. Ben-Moshe T, Dror I, Berkowitz B (2009) Oxidation of organic pollutants in aqueous solutions by nanosized copper oxide catalysts. ApplCatal B: Environ. 85:207-11.
9. Bhaumik A, Haquea A, Karnatia P, Taufiquea MFN, Patelb R, Ghosh K (2014) Copper oxide based nanostructures for improved solar cell efficiency. Thin Solid Films 572:126-33.
10. Evans P, Matsunaga H, Kiguchi M (2008) Large-scale application of nanotechnology for wood protection. Nat Nanotechnol. 3:577.
11. Ren G, Hu D, Cheng EW, Vargas-Reus MA, Reip P, Allaker RP (2009) Characterisation of copper oxide nanoparticles for antimicrobial applications. Int J Antimicrob Agents 33:587-90.
12. Zenou M, Ermak O, Saar A, Kotler Z (2014) Laser sintering of copper nanoparticles. J Phys D: Appl Phys. 47:025501.
13. Longano D, Ditaranto N, Cioffi N, DiNiso F, Sibillano T, Ancona A, *et al*. (2012) Analytical characterization of laser-generated copper nanoparticles for antibacterial composite food packaging. Anal Bioanal Chem. 403:1179-86.
14. Bondarenko O, Juganson K, Ivask A, Kasemets K, Mortimer M, Kahru A (2013) Toxicity of Ag, CuO and ZnO nanoparticles to selected environmentally relevant test organisms and mammalian cells in vitro: a critical review. Arch Toxicol 87: 1181-1200.
15. Liu G, Li X, Qin B, Xing D, Guo Y, Fan R (2004) Investigation of the mending effect and mechanism of copper nanoparticles on a tribologically stressed surface. Tribology Lett. 17 (4), 961-966.
16. Karlsson HL, Cronholm P, Gustafsson J, *et al*.(2008) Copper oxide nanoparticles are highly toxic: a comparison between metal oxide nanoparticles and carbon nanotubes. Chemical Research in Toxicology 21(9):1726-1732.
17. Heinlaan M, Ivask A, Blinova I, *et al*. (2008) Toxicity of nanosized and bulk ZnO, CuO and TiO2 to bacteria Vibrio fischeri and crustaceans Daphnia magna and Thamnocephalusplatyurus. Chemosphere 71:1308-1316.
18. Song MF, Li YS, Kasai H, Kawai K (2012) Metal nanoparticle-induced micronuclei and oxidative DNA damage in mice. J. Clin. Biochem.Nutr. 50:211-216.
19. Fahmy B, Cormier SA (2009) Copper oxide nanoparticles induce oxidative stress and cytotoxicity in airway epithelial cells. ToxicolIn Vitro. 23(7): 1365-1371.
20. Melegari SP, Perreault F, Costa RH, Popovic R , Matias WG (2013) Evaluation of toxicity and oxidative stress induced by copper oxide nanoparticles in the green alga

Chlamydomonasreinhardtii. Aquatic Toxicology, 143: 431-440.
21. Wang Z, Li J, Zhao J, Xing B (2011) Toxicity and internalization of CuO nanoparticles to prokaryotic alga *Microcystisaeruginosa* as affected by dissolved organic matter Environmental Science & Technology 45: 6032-6040.
22. Gómez J, Martínez-A C, González A, Rebollo A (1998) Dual role of Ras and rho proteins: At the cutting edge of life and death Immunology and Cell Biology 76 : 125-134.
23. Wang Z, von-dem-Bussche A, Kabadi PK, Kane AB, Hurt RH (2013) Biological and environmental transformations of copper-based nanomaterials ACS Nano. 7: 8715-8727.
24. Griffitt RJ, Weil R, Hyndman KA, Denslow ND, Powers K, Taylor D, Barber DS (2009) Exposure to copper nanoparticles causes gill injury and acute lethality in zebrafish (*Daniorerio*) Environ Sci Technol. 41:8178-8186.
25. Aruoja V, Dubourguier HC, Kasemets K, Kahru A (2009) Toxicity of nanoparticles of CuO, ZnO and TiO2 to microalgae *Pseudokirchneriellasubcapitata*. Sci Total Environ. 407(4): 1461-1468.
26. Wang H, Huang Y, Tan Z, Hu X (2004) Fabrication and characterization of copper nanoparticle thin-films and the electrocatalytic behavior. Anal ChimActa. 526(1): 13-17.
27. Bancroft JD, Gamble M (2001) Theory and practice of histological techniques, 5th Ed. Churchill livingstone 281-285.
28. Gupta YR, Sellegounder D, Kannan M, Deepa S (2016) Senthilkumaran B., Basavaraju Y., Effect of copper nanoparticles exposure in the physiology of the common carp (*Cyprinuscarpio*): Biochemical, histological and proteomic approaches Aquaculture and Fisheries. 1(1): 15-23.
29. Chen Z, Meng H, Xing G, Chen C, Zhao Y, Jia G, Wang T, Yuan H, Ye C, Zhao F, *et al*. (2006) Acute toxicological effects of copper nanoparticles *in vivo*. Toxicol.Lett. 25:109-120.
30. Sizova E, Miroshnikov S, Polyakova V, Gluschenko N, Skalny A (2012) Copper nanoparticles as modulators of apoptosis and structural changes in tissues. J BiomaterNanobiotechnol. 3:97-104.
31. Ibrahim M A, Khalaf A A, Galal M K, Ogaly H A, Hassan A H (2015) Ameliorative influence of green tea extract on copper nanoparticle-induced hepatotoxicity in rats. Nanoscale Research Letters 10: 1-9.
32. Al-Bairuty GA, Shaw BJ, Handy RD, Henry TB (2013)Histopathological effects of waterborne copper nanoparticles and copper sulphate on the organs of rainbow trout (*Oncorhynchusmykiss*) AquatToxicol. 126:104-115.
33. Ostaszewska T, Chojnacki M, Kamaszewski M, SawoszChwalibóg E (2016) Histopathological effects of silver and copper nanoparticles on the epidermis, gills, and liver of Siberian sturgeon. Environ. Sci. Pollut. Res. 23: 1621-1633.

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