The health effects of nanoparticles NPs (are raising considerable and growing concerns from the public and government around the world). Nanomaterials are new forms of material with special properties, but are characterized by having a particle size of less than 100 nm. Copper is an essential trace element and its deficiency leads to different diseases in humans. In general, copper NPs have been reported to cause damage to tissues and organs. The toxicity of nano-copper depends on sex. The increase in the production of reactive oxygen species ROS (and reactive nitrogen species RNS (plays an important role in copper-induced organ damage). 

In this review, we will summarize the effects of nano-copper on the body by inducing apoptosis. Copper is a necessary traceable element and its lack is resolved in various diseases in humans. On the other hand, it acts as a catalytic cofactor in certain redox enzymes required in a broad spectrum of metabolic processes. When copper intake exceeds the tolerable limit, it shows toxic effects that lead to cell death. Nano-copper research has shown great promise as drugs for the treatment of osteoporosis, antibacterial agents, additives in cattle and poultry, and the intrauterine contraceptive device.

At present, biosecurity and the nano-copper research team have launched a preliminary investigation and the result showed that there was potential toxicity in both human and ecological systems. In fact, copper is abundant in the human body, but copper overload in vivo can cause toxicological activities. Compared to commercial and micro...
copper, nano copper can cause serious toxicological effects and the kidney and liver are target organs of copper NPs [8, 9]. Recently, copper NPs are used as additives in lubricants, polymers/plastics, coatings and in catalytic reactions to the excellent reactivity of NPs copper, the lubricating oil is added as an additive to effectively reduce friction and wear or to repair worn surfaces.

Copper NPs are deposited evenly on the graphite surface to significantly improve the loading structure load, coulombic efficiency, cycle characteristics and high performance as an anodic lithium ion material [6]. Nano-copper composites have a range of industrial applications [4]. Some studies have shown that environmental copper is toxic to Cyprinus carpio and causes a response to stress, sodium loss, tissue damage of the liver, increased oxidation, oxidative stress and metabolic disorders [10, 11]. In general, copper NPs have been documented as one of the most toxic nanoparticles in mammals, as indicated by inflammation in mice exposed sub-acute [12].

The in vivo uptake and distribution of biomolecules such as Saccharomyces cerevisiae, Listeria, Escherichia coli and Staphylococcus aureus in the liver, copper NPs, like other nanomaterials, can enter the environment and the human body through different routes, such as venous blood, during shipping and consumption of products and disposal, and so on [13]. Although we have identified the potential risks of copper NP in human health, its subacute toxicity has not been described.

**Nano copper toxicity**

The I.D. 50 values of nano-copper is 23.5 mg/kg of body weight and are considered to be extremely toxic to animals. Nano-copper toxicity may be related to in vivo ionization. The reason for this appears to be that the particles of the copper nanoparticle are more likely to collide with the bio-substances in vivo. For nanometric-sized copper particles, a large surface leads to ultra-high reactivity. NPs copper reacts drastically with H+ in the gastric juice and can lead to a massive form of HOCl, which is extremely toxic to the kidney due to kidney disorders. Excess HOCl in vivo becomes a cause of metabolic alkalosis, which becomes the origin of the symptom hypopnea and the electrolyte pathologies produce toxic substances observed.

In vivo hemostasis continues to be copper ionization. Therefore, the study suggests that ionic copper and nano copper have different effects on fish. Therefore, enter the body of the fish by different routes of different sizes, generating different effects with different sizes in the blood of copper, ceruloplasmin, iron and ions. Copper, sodium and iron chloride in plasma suggest that Gill is the main site for absorption of ionic copper, while nano-copper can be absorbed through the intestine [15]. Nano-copper NP can not directly involve m ice, however, causing an excessive accumulation of alkalizing substances and heavy metal ions copper ions, the blood infection of m etabolic alkalosis and overload of copper ions [16].

Further, the toxicity of nano-copper depends on several factors: the size of the nanoparticle, the toxic substances and the exposure time. For example, a single exposure to nanometric copper is less toxic than an exposure after being exposed to the same amount of particles [17]. The reason for the difference in the distribution, penetration and tissue damage of NPs in several studies could be due to different methods of synthesis, which lead to a size, shape and other different physical and chemical properties of NPs. Therefore, the interaction and impact of NPs on animal cells and tissues will vary [17]. Several studies support the fact that increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNAP) plays an important role in copper-induced organic dysfunction. Exposure to NPs of copper caused altered levels of intracellular production of ROS and NO [18]. Changes in the structural and chemical properties of NPs can end up with changes in biological activity, including ROS generation. Oxidative stress induced by NPs is the result of cellular factors, size, particle surface and presence of metals, while cellular responses such as mitochondrial respiration, cell interaction and immune cell activation are responsible for them. EDTA is added to the blood from ROS. NPs-induced oxidative stress responses have implications and other pathophysiological effects that include genotoxicity, inflammation, and fibrosis as evidenced by the activation of associated cell signaling pathways [18]. Exposure to NPs is likely to occur with microbial agents and the defense of the innate host by neutrophils and is fundamental in the control of bacterial elimination in the host [19]. It is of fundamental importance to maintain neutrophil concentrations...
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At appropriate physiological levels [20]. Recently, it has been reported that copperNP, compared to other NP metal oxides, is highly toxic under in vitro conditions [21]. Recent research on copper NP after subcutaneous injection has shown that the regulatory effects of NP on organisms depend on the dose used [22].

To investigate the mechanism of nanotoxicity of copper NPs it is possible to provide a detoxification solution. Timing and appropriate clinical therapy, containing detoxification due to heavy metal overload and correction of acid-base imbalance, is required when acute intoxication is verified by the gastrointestinal tract [23]. The strategy can be deduced from studies on metal toxicity due to the fact that most non-valence metal particles are easy to oxidize to ionic acids in acidic solution even if they are inactive in vivo.

**Hpa btx icity**

At some dose of copperNP 341mg/kg, steatosis was observed around the central veins of the liver tissue of experimental mice. This pathological examination revealed that the kidneys, the liver and the spleen are the target organs for copperNPs. These were also shown by measurement of the biochemic blood index KBN, Cr, ALP and TRA (which reflects the renal and hepatic function of experimental mice) [1]. In one study, the effects of intraperitoneal injection of various doses 10, 100 and 300mg/kg of copper NP on the liver and the perfum of liver enzymes in rats were investigated [24]. Histology of the lungs showed thickening of the airway wall and intensified fibrous tissue in all groups. Hepatic histology also showed vascularization in the central veins and vessels of the portal triad, and the disappearance of the liver hexagon lobules in the three treatment groups receiving different doses of copperNP. Results of the biochemical analysis of liver enzymes showed that the mean SGOT enzyme was 200 days after the injection, in the 10 mg/kg and 100mg/kg group of copperNP were significantly higher than those in the control group. On day 14 after surgery, a significant difference was observed between the groups receiving 300 and 100mg/kg of copperNP. Furthermore, the level of SGPT was significantly higher in the group that received 100mg/kg compared to the group which received 100mg/kg. Recently it has been reported that 3 hours after the injection of copperNP 2mg/kg into them, these NPs could be observed in the vascular areas of the periportal hepatocytes and in the cytoplasm of the Kupffer cells of the liver of the treated rats. Furthermore, they disappeared within 3 days after treatment [25]. Apoptosis can be observed in the periportal epithelium of the hepatic tubule and kidney after 3 days and 3 hours, respectively, by 3 injections of copperNP [25].

Doudi et al. has indicated that all copperNP concentrations induce toxicity and changes in the histopathology of rat liver and pulmonary tissues [24]. Therefore, they can not be used by human because of their toxicity. Exposure to nano-copper increased ROS production, one of the most frequently reported toxicities associated with NP. Studies on them showed that the expression in mitochondria was potentiated by copperNP and subsequently helped to release cytochrome C from the mitochondria to the cytosol. Nano-copper can trigger both intrinsic and extrinsic apoptotic pathways in oxidative stress [26].

**Spbln btx icity**

Copper NPs causes severe atrophy and color variations in the spleen, and research indicates that copper is induced by copperNP. On the other hand, collectors of copperNP treated with copperNP exhibited a blackish color at necropsy[1]. Th is is NP induces the reduction of splenic units, the decrease of lymphocytes and splenic interstitial fibrosis [1].

**N pph o btx icity**

In one study, morphological changes of kidney in mice exposed to copperNP 1080mg/kg showed dramatic changes in color and transformation of bronze [1]. Damage of the renal tubules was observed in mice exposed to copperNP. In the kidney, the glomerulus was reduced and ellen in the light of Brown’s capsule, indicating glomerulonephritis [1]. One investigation demonstrated both the toxicity and the kidney damage and the liver induced by nano-copper and verified that these signals were similar to those of their in vivo soluble copper equivalent [27]. Exposure with copperNP increased levels of formaldehyde MDA (and carbonylation of proteins in the renal tissue of experimental animals) [18]. NP copper exposure in one study intensified glutathione disulfide GSSG (levels, reduced glutathione GSH (and
thus reduced the GSH/GSSG ratio in the renal tissue of experimental animals [18]. In addition, podocytes called visceral glomerular epithelial cells contributed to the glomerular filtration barrier and were the target of lesions in many glomerular diseases. Numerous studies have shown that oxidative stress is a significant mediator of podocyte lesions [28]. When the kidney was injured, the podocytes changed, including the retraction of the foot processes and also the loss of cells, and then gave rise to many glomerular diseases. In a study in which the podocytes were analyzed with nano-copper, the viable cells were reduced with the concentrations and the increased period. In this study, viability was 1.40% when the nano-copper level reached 100 μg/mL for 24 hours. Concentration of 100 μg/mL seemed too high and toxic, so the concentration of 1, 10, and 30 μg/mL was selected to detect the cytotoxic effect of nano-copper, thereby increasing ROS as observed in podocytes of the nano-copper group and were in a positive part of the dependent concentration. Meanwhile, T½-SD products were significantly reduced when they were treated with nano-copper in podocytes [29]. A commonulate evidences suggests that oxidative stress also played an important role in the mechanism of podocyte injury. Podocyte lesions accompanied by reduction of nicotinamide adenine dinucleotide phosphate oxidase induced by increased renal oxidative stress [30]. ROS, including superoxide anions, hydrogen peroxide, hydroxyl radicals, etc., had a higher reactivity than molecular oxygen. If present at high levels, ROS may cause DNA damage to nuclear DNA and alterations in proteins, lipids, and carbohydrates. Superoxide dimutase 1 (SOD), as one of ROS's enzymatic scavengers, can combat the aggregation of ROS and limit oxidative DNA damage. In other words, the SOD activity level is related to the antioxidant capacity [29, 31, 32]. The researchers reported that SOD could suppress apoptosis and reduce ROS usually corresponds to an increase in cell death in apoptosis [33]. The relationship between ROS and SOD levels observed in nano-copper-treated podocytes indicates that free radicals were generated by exposure to nano-copper. All of the above has shown oxidative-antioxidant stability of nano-copper and cytotoxicity in podocytes [29, 33, 34].

Current results showed that nano-copper MDA levels in podocytes markedly increased, causing peroxidation of lipid cell positions and confirming that cellular DNA damage induced by nano-copper by oxidative stress. In addition, when previously treated with N-acetyl-L-carnosine, the type of ROS sequestering, nano-copper-induced apoptosis induced podocyte [29]. Th ese results demonstrate that increased oxidative stress was an important mechanism in nano-copper-induced podocyte damage.

Pulmonary toxicity

Th e eNP that is elit inhaled through the respiratory tract from th eucociliated escalator can be ingested in the gastrointestinal tract [1]. Kim, J.S., et al. Th ey recorded that IN Cu caused strong inflammatory reactions that iron oxides JFe, titanium JTi, silver AG with m proved total cells and neutrophils at the lungs recruit em, as well as increased total activity of proteins and lactate dehydrogenase ) IDH ( in fluid bronchoalveolar lavage BAL ). J35. However, cytotoxicity and DNA damage has been demonstrated in the lung epithelial cells of type II A 549 all the metal oxide particles analyzed CuO, TO, ZnO, FeO, and Fe3O4 at 40 and 80 μg/mL J36. Both inhalation exposure systems, such as instillation, have been identified. Several studies have shown that inhalation was most effective in affecting the inflammatory response, collagen deposition, oxidative stress and fibrosis J37, 38]. Th e eN port role of chemo kines/cytokines and immunology of cells for bacterial infections and pulmonary inflammation has been demonstrated in recent studies J39, 40. Th e necrosis factor JNF-α is an important early cytokine required for neutrophil recruitment. M. monotone chemoattractant protein MCP-1 may also amplify the recruitment of neutrophils and macrophages in the lung. Th ese increases are consistent with a high number of macrophages and neutrophils in bronchoalveolar lavage BAL ( and histopathological evaluation of lung tissues ofm ice exposed to CuJ alveolitis and perivascularitis J35, 41]. Th e key functions of neutrophil inflow against bacterial infection in the host defense system are controversial. Contents Recruitment of neutrophils causes a decrease in bacterial clearance, while an excessive flow of neutrophils can cause severe lung inflammation and neutrophil-mediated damage that could cause reduction of lung clearance J42. Recent data also show that exposure to CuNP through instillation and inhalation of attenuated bacteria in oval of the lung, although there has been strong inflammation J35]. Th erefore, exposure to CuNP may increase the risk of lung infection affecting host defense against bacteria.
Gastrointestinal tract is also considered as a possible absorption portal. There are many ways in which NPs can be ingested in the gastrointestinal tract. The absorption of particles of different sizes through the gastrointestinal tract can also end up in various toxic effects. Although NPs may contact the respiratory organs, however, other organs such as the gastrointestinal tract should be considered because NPs can enter the gastrointestinal tract in many ways and indirectly through them uscosa or directly via the oral route. [44, 45].

Nano-copper clearly showed systemic effects of food channel dysfunction, loss of appetite, diarrhea and vomiting. [1] Nano-copper can be translocated light intestinal tract containing lymphatic intestinal tissue Peyer's plaques IPP (and M cells) specialized phagocytosis enterocytes. Furthermore, copper can promote phagocytosis in the gastrointestinal mucosa and produce mononecrotic responses. Emediated by antigens. [46]. Consistency can be directly linked to the route of exposure and the physico-chemical properties of the nanoamplitude) for example, type, size, structure, surface modification, crystalline phase. The oral route is relatively simple toxicological process can be compared to the pulmonary route. [7]. On the contrary, copper is not distributed in the stoma. Copper is less reactive than hydrogen ions H⁺ (of gastric juice and can quickly be reduced). Copper is also a chemical process caused by an ionic copper overload in vivo. Because the ultrafine NPs of copper nanoparticles are highly active in the biological systems when they are in the stomach. NPs particles cause the accumulation of copper highly alkaline substances and excessive copper ions concludes with etiologic alkalosis and copper overload. [16]

In one study, the appearance of the stomach of mice exposed to nano-copper and presented a cyan color. The result of nano-copper suggests that it may have a role in the stomach longer. In other words, the lasting interaction with the acidic juice can cause the persistent production of high-energy etal ions in vivo. [7, 9]. Nano, micro, and copper ions show different biological characteristics in vivo through routine oral exposure. With regard to nano-copper particles, both metabolic alkalosis and copper overload contribute to its severe toxicity. Unlike this, micro-copper does not stagnate in the stomach and the ionization rate is much lower than that of NPs. After the particles have been pushed into the small intestine, the ionization reaction is prohibited due to the presence of fatty acids. For direct ingestion of copper ions, the molar porosity of the intestinal epithelium and the enteral canal disturbance occur in experimental animals. These toxicological responses can be partially corrected within 72 hours. [7].

Nanotoxicity, genotoxicity and carcinogenicity

In the first carcinogenicity and genotoxicity studies of copper-soluble copper compounds, such as copper sulfate, they were genotoxic, with functions including induction of chromosome aberrations and micronuclei. Leghorn white chickens and chromosome aberrations in Swiss white mice. [47, 48]. It has now been documented that different NPs elicit different responses from different cell lines or biological systems. [49]. Copper NPs have been shown to be extremely reactive in a simulated intracorporeal environment. [50]. Studies have shown that copper NPs can interact with DNA. This was shown by an in vitro study in which NPs 4-5 nm (dependent degradation caused dose of isolated DNA, monosomes to generate single oxygen) 9 and 37 and Hela cells. [51]. NPs copper and its compounds caused a variety of effects, including oxidative stress, cytotoxicity, neurotoxicity, DNA damage, and DNA lesions in a variety of cell lines. [49].

DNA damage has been documented as a result of oxidative stress, controlled by elevated 8-isoprostan levels and the percentage of glutathione disulfide $(GSSG)$. (Total glutathione in respiratory epithelial cells in humans with age is higher). High oxidative stress can cause DNA damage to DNA, which in turn has the potential to be carcinogenic [26, 49]. In another study on A 549 cells, copper oxide NPs were the most potent with respect to cytotoxicity and DNA damage. [36]. Copper NPs <100 nm were reported to be more toxic to human A 549 cells than copper particles and were also shown to induce sensory neuronal toxicity. [52]. The size, surface chemistry, surface area, and morphology and reactivity of particles in the soluble particle are key factors that must be
clarified to accurately assess the toxicity of NPs. NANO-copper in arterial appears to be toxic not only for DRG neurons but also for glial cells. Recently, the results showed that at 10 and 20 μM, copper NPs did not show significant toxicity in DRG neurons. Th is could be due to differences in the properties of copper and NP pure copper NPs and could also be due to the nature of cells in different studies and the duration of exposure to NP. [52]. A recent report showed dose-dependent toxicity [10-100 μM] in human H4 glial cells exerted by NP of cupric oxide. [53]. Th ese NPs of copper oxidewh ich neurons would inhibit mitochondrial dehydrogenases and cause ROS generation. Several studies have demonstrated cytotoxicity resulting from the primary induction of lipid peroxidation of am mitochondrial membrane of am et al that can lead to the breakdown of electron transport, the decoupling of oxidative phosphorylation and decreased mitochondrial membrane potential. [54, 55]. Said that the neurodegeneration associated with copper overload in Wistar disease can cause mitochondrial damage, increased ROS production and failure of antioxidant defense system. [56]. Copper can also induce oxidative stress by reducing glutathione levels in neurons. Copper NPs enter the cell, so they can attack mitochondria and cause an increase in oxidative stress. [57]. Prabhu, B.M., et al. have shown that exposure to copper NPs has led to significant toxicity for DRG neurons grown at concentrations of 40-100 μM but not at 10-20 μM. However, exposure to NP of copper size 40 μm, 60 μm and 80 μm had toxic results in DRG neurons, 40 μm copper NPs and 60 μm size had a higher toxic result of 80 μm particles in TH eerefore, the toxic effect seems to depend on concentration and size. Th e mechanism that correlates the toxicological effects followed with the exposure of DRG neurons to copper NPs may be oxidative stress. [52].

Unresolved inflammation can cause aberrations and DNA abnormalities that are known to be carcinogenic. Yang et al. used rat model to study the mechanism of hepatic toxicity induced by copper NPs with the identification of hepatic gene expression profiles that were phenotypically correlated with conventional toxicological outcome. [58].

Copper NPs have also been shown to be neurotoxic and neurotrophic. However, apart from the induction of other types of pathology, none of these studies reported carcinogenesis. In general, changes in apoptosis, gene expression, oxidative stress and persistent inflammation were the main effects of copper-based NPs that may predispose to carcinogenicity.

B. bovis major ines

Pathological examinations and morphological changes indicate that the kidney and liver are two important target organs for copperNP through the oral route. Therefore, the biochemical parameters of blood (BUN, Cr, TBA and ALP) that reflect renal and hepatic function are more prominent. In one study of all ice exposed to NP, these four biochemical indices were significantly higher than the control group. An early sign of BUN and Cr is particularly obvious. [1]. Increased triglycerides in serum, liver and renal tissues could be considered an important sensitive index reflecting lipidosis caused by nano-copper. To date, it is unclear whether nano-copper can enter the bloodstream through the entire gastrointestinal lining. [27]. Th e increase in the pH of the blood causes a compensatory reaction: (a) the respiratory compensation is naturally caused by several inutes. However, respiratory compensation is limited, as high PaCO₂ and low PaO₂ should stimulate the apneustic center to prevent hypoxia, therefore, PaCO₂ was only partially raised 24 hours after exposure; (b) In theory, renal clearance begins relatively late, but can be maintained for a long time. [7, 59, 60].

Unlikely iccro-copper, nano-copper could cause a high level of serum copper. [56]. An index of acute toxicosis. More prominently, nano-copper has a low elimination frequency in vivo, which can worsen heavy metal toxicity. Itm attains a high level of Cu in the nano group even at 72 hours, suggesting that ic copper carries high persistent copper concentrations in the blood, possibly eventually ending up in a fatal copper overload. [7, 61].

Nano-app erand apop sis

Bcl-2 proteins are regulatory upstream of the mitochondrial membrane. From immuno blotting, it was observed that pro-apoptotic Bax regulated protein increased nano-copper and anti-apoptotic Bcl-2 protein reduce m. mitochondrial membrane potential. A apoptotic cell death causes oxidative stress directly related to mitochondrial dysfunction. A alteration of mitochondrial membrane potential, cytochrome c release in the cytosol and possibly activation of caspase 3 are known markers related to cell death induced by oxidative stress via dependent m -onochondrial pathway. [57]. Th e influence of Bcl-2 family proteins in mitochondria regulates mitochondrial...
dependent cell death]62[. From unobtained analysis showed that nano-copper poisoning leads to high levels of cytosolic cytochrome c, A paf 1 caspase 9 and caspase 3 cleaved. Now research has shown that nano-copper exposure significantly increases the cellular level of Fas protein, (caspase 8) protein and TP53 protein. 18[

The increase in the ROS level induces a cascade of pathways that in turn activate the transcription of several genes; those genes change the regulatory pathways of cell survival and eventually lead to apoptosis. Apoptosis could be mediated by dependent and independent mitochondrial pathways. Tests suggest that the variation of mitochondrial membrane potential could alter the cells involved in apoptotic death through cascades sensitive to oxidative stress signaling via mitochondrial dependent.]63[.

When decreasing the expression of Bcl-2 proteins and the Bax protein expression is proved, there will be a decrease in mitochondrial membrane potential due to rupture of the mitochondrial membrane.]18[Th e extrinsic pathway is triggered by a cell death receptor (Fas, TNF, etc.), which initiates a signaling cascade mediated by the activation of caspase-8.

CONCLUSION

The rapid growth of nanotechnology suggests that it will soon find widespread application in everyday consumer products and in new pharmaceutical, electronic and other industries. When copper intake exceeds the tolerable limit, it exerts toxic effects that lead to cell death. This is due to the toxic effects that lead to cell death. The increase in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays an important role in copper-induced organic dysfunction. All NP copper concentrations cause toxicity and alterations in the histopathology of the liver and pulmonary tissues of rats. The increase in oxidative stress is a fundamental mechanism in the damage of podocytes caused by nano-copper. Nano-copper can pass from the lung of the intestinal tract through aggregations of intestinal inflammatory tissue. Peyer patches (PP) (containing macrophages and lymphocytes) initiate the innate immune response. When they are introduced into the stomach, the nano-copper particles react with hydrogen ions in the gastric juice and can quickly become ionic. The liver and kidneys are two target organs for exposure to NP copper via the oral route. Compared to micro-copper, nano-copper could obviously induce more levels of serum copper SC, a marker of acute toxicity. Now research has shown that nano-copper exposure significantly increases the cellular level of Fas protein, (caspase 8) protein and TP53 protein.

It will be important to continue the interpretation of laboratory data in the clinical context of the patient to understand emerging technologies. At the same time, a growing understanding of the mechanisms that drive the toxicity of this NP will improve the classification, prognosis and treatment of patients with NP copper toxicity.
CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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