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# Mechanism Of Toxicity Of Copper Oxide Nanoparticles. A Review Study.

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**Abstract**
Copper is an essential trace element and has important role in many metabolic and chemical processes in cells and tissues.Due to their flexible properties, copper-based nanoparticles have been used in many industrial, chemical, electronic and medical applications. As a result of these wide applications exposures of human to these nanoparticles are increased. Oxidative stress and reactive oxygen species (ROS) production are considered the main mechanism by which copper oxide nanoparticles (CUONPs) induce toxicity. Brain is most susceptible to toxicity by CUONPs due to its high content of unsaturated fatty acids and to the relative paucity of antioxidant enzymes in the brain tissue compared with other organs.

**Keywords:**
copper, copper oxide nanoparticle, toxicity, neurotoxicity

## Introduction

Nanotechnology is a rapidly growing revolutionary field that deals with the synthesis, properties and applications of nanomaterials. Due to their distinctive physicochemical and electrical properties, nano-sized particles have gained great attraction in various field as in electronics, biotechnology, and aerospace engineering [1].

Nanoparticles (NPs) are ultrafine particles that are defined by the international organization for standardization as nano-objects with size ranging from 1 to 100 nanometers [2]. Reducing particle size provides an increased surface area and modifies unique and specific physicochemical properties such as high conductivity, strength, durability, and chemical reactivity compared to bulk materials [3].

Several studies reported that NPs have greater toxic effects on human health as penetration of the cell membrane and alteration of many important cell functions [4]. Other reports revealed that NPs cause injury to the vascular endothelial cells and they can pass the blood-brain barrier causing toxic effect on the brain. Also, NPs cause many adverse effects on many organs such as liver, kidney, lung and gonads [5]

CUONPs appear as brownish-black particles. They are of great interest due to their easiness of preparation, their wide use in different applications and as they are harmful to humans and dangerous for the environment with adverse effect on the aquatic life [6]. (fig.1)
Many studies reported the hazardous effects of CUONPs on different organs of the human body specially the brain. It was suggested that these particles might have potential toxic effects on the central nervous system. The postulated mechanism of their toxicity is that these particles produce oxidative stress, cytotoxicity, and mitochondrial dysfunction that induce apoptosis [7].

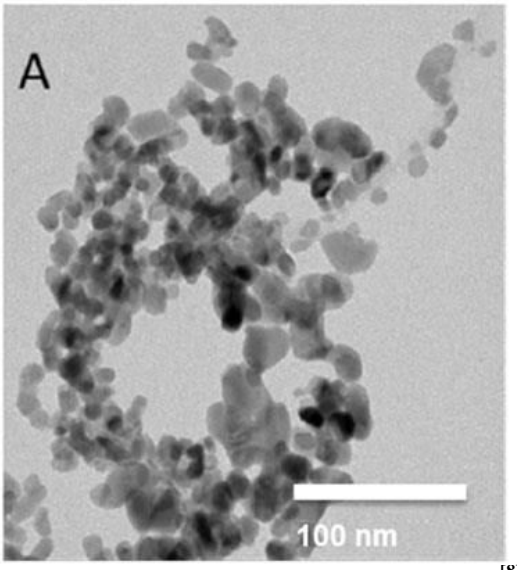


**Fig. 1**. (A) TEM image of nano-sized CUONP. [8].

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**Preparation and Synthesis of CUONPs**

In nanotechnology, the advancement of controlled amalgamation of nanoparticles with very much defined shape, size and structure is a major challenge. In the last ten years, synthesis of CUONPs has gotten extensive consideration because of their special physical and chemical properties that are different from the bulk substances. It is significantly advanced because of their important industrial and biomedical applications. Synthesis technique is important for the properties of the final nanosystem, since it may control the size and morphology of the nanoparticles, so acquiring characteristic differ from the bulk solid material[9].

The arrangement of copper nanoparticles is much more difficult in correlation with respectable metals due to the likelihood of oxidation of copper with air. Metallic copper nanoparticles have gotten much consideration when contrasted with all other respectable metals for example; Ag, Au and Pt due to their little size, high surface/volume proportion, improvement of size, shape and oxidation obstruction, etc. [10].

Copper nanoparticles tend to get oxidized when they are presented to air and agglomeration of particles occur due to surface oxidation. To dodge this issue copper nanoparticles are created in a dormant gas atmosphere and coated with organic and inorganic coatings as silica and carbon. Now and again, defensive polymers, or surfactants are used to repress oxidation [11,12].

There are various techniques for synthesis of CUONPs, which classified into chemical methods (bottom up) and physical methods (top down). Some of the methods like sonochemical reduction, electrochemical, chemical reduction, microemulsion techniques, hydrothermal, sol–gel synthesis, polyol process and microwave-assisted methods are the major techniques for synthesis copper nanoparticles from bottom-up approach [13].Top down methods include mechanical milling, vapor phase synthesis, laser ablation, and pulsed wire discharge (PWD) [14].

Physical method of preparing nanoparticles requires expensive equipment, high temperature and vacuum frameworks. Biological methods are treated as bottom up technique, which use bacteria, fungi, and plant extracts but due to shortage of knowledge and experience, it is not commonly used. Chemical methods are utilized for preparation of nanoparticles due to its ease, low cost, high flexibility, simple accessibility of types of gear, no need of vacuum frameworks, environment friendly and gives high return in surrounding conditions [10].

The most common and suitable chemical approaches are the microemulsion and electrochemical techniques. Microemulsion got extensive consideration on account of its capacity to control the shape and size of particles by the use of legitimate microemulsion and by the surfactant adsorption, however, it uses large concentration of surfactant and it is expensive[15].

The most remarkable focal point of electrochemical method is the capacity to control the morphology and size of the subsequent CUONPs by adjusting the temperature, time, current thickness, creation or voltage [16].

Laser ablation, aerosol techniques, and radiolysis are common physical methods to synthesize copper oxide nanoparticles but the use of expensive instruments and excessive energy consumption makes these methods less popular [17].

Biosynthesis of nanoparticles was created to defeat the issues of chemical and physical synthesis like expense and hazardous chemicals. Biosynthesis of copper nanoparticles is considered as chemical or bottom up technique. Plants are the most cost effective and environmentally friendly source for production of copper oxide nanoparticles. As they are easily available, various plants are used to produce copper nanoparticles such as extract of plant T, Arjuna, Mangolia. Pseudomonas Stutzeri bacteria and morganella bacteria are reported to be used for synthesis of these nanoparticles. Besides, fungi such as Penicillium and Aspergillus species have been reported to synthesize copper nanoparticles with unique morphology [18].

**Properties of CUONPs**

**Azonano** [19] demonstrated the chemical, physical and thermal properties of CUONPs as shown in the tables:

Chemical Properties

| **Chemical Data** | |
|---|---|
| **Chemical symbol** | **CUO** |
| **CAS No.** | **1317380** |
| **Group** | **Copper 11, Oxygen 16** |
| **Electronic configuration** | **Copper [Ar] $3d^{10}$ $4s^1$,<br>Oxygen [He] $2s^2$ $2p^4$** |
| **Chemical Composition**<br>**Element** | **Content** |
| **Copper** | **79.87%** |
| **Oxygen** | **20.10%** |

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Physical Properties

| Properties | Metric | Imperial |
|---|---|---|
| Density | 6.31 g/cm$^3$ | 0.227 lb/in$^3$ |
| Molar mass | 79.55 g/mol | - |

Thermal properties

| Properties | Metric | Imperial |
|---|---|---|
| Melting point | 1201$^o$c | 2194$^o$f |
| Boiling point | 2000$^o$c | 3632$^o$f |

CUONPs have been characterized by ultraviolet-visible absorption spectroscopy, X-ray diffraction [20], scanning electron microscopy [21], transmission electron microscopy [22], atomic Force Microscopy and infrared spectroscopy[23].

**Applications of copper oxide nanoparticles**

Copper oxide (CUO) has a wide range of applications in various fields, from energy conversion and storage through environmental science, electronics and sensor. In industrial fields, CUONPs are widely used as p-type semiconductors and transistors in the design and production of batteries, solar cells, gas sensors and field emitters. Nowadays, CUONPS are utilized as heterogeneous catalysts, antioxidants, drug delivery agents, and imaging agents in field of biomedicine [24].

Copper oxide nanoparticles have antimicrobial and biocide properties so that, they are utilized in numerous biomedical applications [25]. They are semiconductor metals with optical, electrical and attractive properties and they have been utilized for different applications, for example, the improvement of supercapacitors, close infrared channels, in attractive capacity media, sensors, catalysis and semiconductors [26].

They are generally utilized as catalysts because of the large surface- to-volume ratio, continually sustainable surface, and changes in microelectrode potential qualities. Stable copper nanoparticles offer appropriate catalytic properties, which are appropriate for dye reduction because of the number thickness of the particles that increases with the precursor concentration, the molecule shape and organization; the smaller the size of the particle, the greater the catalytic activity [20].

A major risk to human wellbeing is water contamination with microorganisms so disinfectant strategies are increased as few organisms are resistant to older antibacterial agents. Copper nanoparticles have been utilized as a disinfectant for wastewater [27].

Future biomedical utilizations of CUONPs are focused seriously around disease discovery and could introduce potential applications in numerous different zones, for instance, in the identification of infections in the human body [28].

**Li et al.** [29] built up an exceptionally touchy and particular technique for the location of H1N1 influenza infection. The standard of this strategy depends on marking of antibodies by utilizing CUONPs. This methodology was planned a sandwich complex made of CUONPs marked polyclonal immune response, ready to identify and tie antigens spoken to by the H1N1 infection. The technique is an enzymatic chromogenic approach, having a place with the purported catalyst connected immunosorbent examine (ELISA) techniques, and turned out to be exceptionally delicate and quicker, as contrasted and other related strategies.

The impacts of copper nanoparticles on fluorescent materials have been reported. CUONPs may cause fluorescence extinguishing, dye disaggregation, dye aggregation, and fluorescence upgrade. This property might be utilized for biosensing and biolabeling [17].

Copper-based medications are generally used to destabilize tumors and malignant growth cells. Copper nanoparticles may fill in as screening specialists for hemoglobinopathies, for example, β-thalassemia, since the groups encourage with a human hemoglobin freak. High antithrombic action and imaging utilizations of copper nanoparticles have been explored. These materials have also been utilized for directing applications [30].

These nanoparticles show great antibacterial behaviors against both Gram negative and Gram-positive bacteria. Despite the fact that the specific mechanism of the antimicrobial impact related with the utilization of CUONPs is not known, a few of their systems of activity on bacterial cells have been discussed [16].

The antibacterial action of CUONPs is been distinctive relying upon the particularities of microorganism's cells. For example, their cell membranes appear to affect the antimicrobial impact of CUONPs, Gram character being a key viewpoint. It was accounted for that 100% of E. coli cells, which are Gram negative, were murdered when a concentration of CUONPs higher than 9.5% was utilized, while for the Gram-positive species Staphylococcus aureus the killing capacity was lower [31].

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CUONPs can kill E. coli, Pseudomonas aeruginosa, and S. aureus in a time dependent manner and the dose used is the most important factor. CUONPs adsorbed on the cell surface of the E. coli collaborate with the cell membrane and later make harm to the membrane, thus increasing the permeability of the cell membrane and leading to a lessening in the viability of the bacteria in copper oxide solution [32].

In hospitals, CUONPs are widely used because of its antimicrobial activity to destroy more than 99% of Gram negative and Gram-positive microorganisms within 2 h of exposure, if a suitable dose is used. Studies revealed that usage of these nanoparticles decrease the event of hospital acquired infections and the costs related to human service in health care facilities. Bed sheets containing CUONPs are viewed as one of the most fascinating advancements in medical care, as they reduce the attachment of the microbes and so reduce the microbial infections in hospitals [33].

Copper oxide nanoparticles are solvent in water and produce colloidal solution. Furthermore, in biological organizations, large surface area and shape of crystal provide greater reactivity and give grounds of their target specificity [34].

Several studies showed beneficial effects of CUONPs on the skin. The studies conducted on women who used pillowcases and sheets containing CUONPs revealed an improved aspect of the facial skin and an increase in the foot skin elasticity using socks soaked with copper oxide nanoparticles [35].

Another application of these nanoparticles depends in their wound healing ability. Different wound dressings and materials have been created to treat burns and other skin injuries. The healing activity is proved by being carefully corresponded with the capacity of CUONPs to restrict microbial colonization of the regarded areas and to keep away from contamination, while advancing recovery of harmed tissue [36]

**Toxicity of copper oxide nanoparticles**

Different toxic activities appear in vivo and in vitro, when CUONPs are tested on human cells and on various animal models [37]**.** These NPs reach the human body through different routes including inhalation, digestion, skin exposure and intravenous. They are deposited in various organs such as kidneys, lung, liver, heart, spleen and brain [38].

Inhalation is the main route of NPs to enter into the body. NPs penetrate into lungs and interact with the epithelial cells leading to inflammation. The olfactory bulb is one of the dangerous routes for the inhaled NPs to access to other organs of the body such as CNS [39].

The occupational workers are the at-risk population exposed to CUONPs. Industrial emission of NPs takes place in the production of asphalt and rubber. The ability of these NPs to stay in lung tissues for unlimited time is accredited to its tiny size. It ends in production of ROS followed by oxidative stress and inflammatory responses because of sensitization and irritation [40].

Gastrointestinal tract is another potential entrance way for NPs into the body. Once NPs enter GIT through consumption of various food items and drugs orally, they are absorbed through GIT and enter in lymphatic cells [41]. Factors affecting the absorbance of NPs by GIT are surface chemistry, charge, geometry, shape, particle size, substrate and attachment potential to substrates [42]. The unstable NPs are excreted by body while the NPs that can form aggregates block the GIT and leads to death. It has been observed that accumulation varies in target organs like brain, heart, liver and spleen. When the NPs enter hepatic circulation, they become hepatotoxic and cause gradual fibrosis.

They cause ulcers by alteration in the lining permeability, induce dysplasia/ metaplasia by weakening the epithelium, malabsorption and in severe conditions results in chronic bleeding. [43].

Hair follicles and sweat glands makes the skin more susceptible to the entrance of NPs. When the protective layer of skin is wounded or removed, there are more opportunities for CUONPs to penetrate it. They may cause different reactions such as irritation, allergy or damage to the cellular or subcellular parts of the body, which may produce chemical reaction causing production of ROS [41]**.**

In vitro researches shown that Cu and CUONPs have particular high toxicity when compared to many other bulk metal and metal oxide nanoparticles. [44] revealed that CUONPs displayed the highest potency in causing DNA damage and cell death when compared to several metal oxides such as TiO2, ZnO, CuZnFe2O4, Fe3O4, Fe2O3 after exposure of A549 cells (Figure 2).

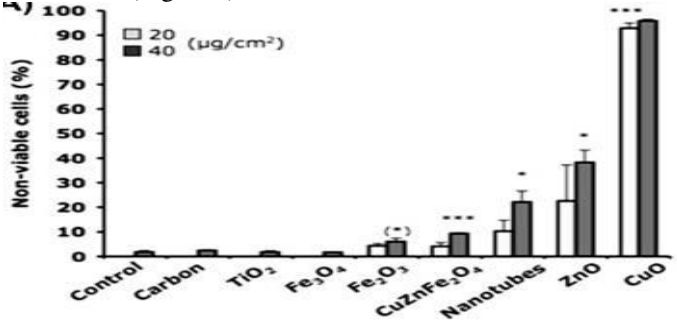


**Fig. 2**. Large variation in toxicity induced by various metal oxide nanoparticles[44]

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**Lanone et al.** [45] who compared the toxicity of twenty four nanoparticles in macrophage (THP-1) and A549 cell lines by utilizing two different cytotoxicity assays and at two different points of time (3 and 24 h) showed that CUNPs and zinc NPs, were the most toxic nanoparticles. Furthermore, **Sun et al.** [46] compared the toxicity of several metal oxide nanoparticles (CUO, TiO2, SiO2, Fe3O4or Fe2O3) in three different cell lines and showed that CUO was the most toxic one.

A549 cells treated with CUONPs showed significant increase in autophagy thus indicating that one of mechanisms of cytotoxicity of CUONPs may involve the autophagic pathway in A549 cells [46].

One of mechanism by which CUONPs induce their toxicity is called Trojan horse-type mechanism which stated that the solid particle structure allows high uptake of Cu, and the resultant release of copper ions within the cells lead to high toxicity. Copper ions are redox active and their high concentration inside the cells causes great oxidative stress to them in form of induction of catalase and superoxide dismutase (SOD), oxidative DNA damage, formation of intracellular ROS, and depletion of glutathione[28, 44] .

After exposure to CUONPs there is decrease in the cell viability in different human cells. CUONPs disturb the nuclear membrane, allowing the particles to enter inside the nucleus causing direct damage to DNA [47].

The major mechanisms of CUONPs toxicity are oxidative stress and ROS generation. CUONPs cause toxicity via direct and indirect ways. The direct way includes activation of ROS production and the indirect pathway is by stimulating redox system of cell which leads to ROS production [1]. (Fig. 3).

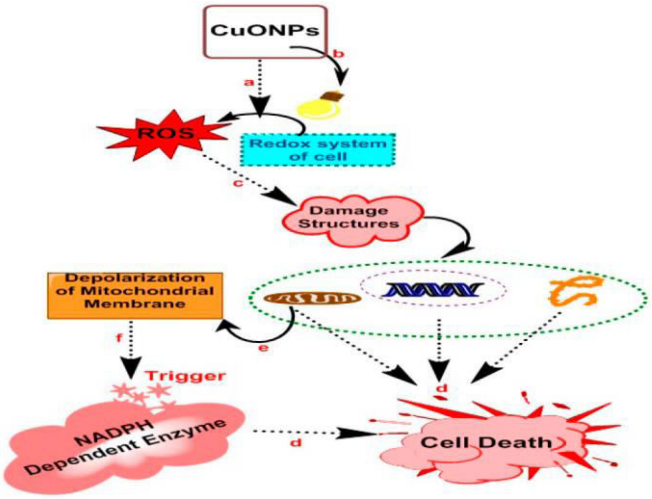


**Fig. 3** Mechanism of action involved in the cytotoxicity of CuO NPs comprises of multiple steps **(a)** Production of ROS directly via exposure of CUONPs, **(b)** Stimulation of redox system of cell that leads to production of ROS, **(c)** Generation of ROS ultimately leads to damage structures like mitochondria, DNA, proteins and so on, **(d)** Damaged structures promotes cell death, **(e)** Damages to mitochondria involve depolarisation of mitochondrial membrane, **(f)** Depolarised mitochondrial membrane trigger NADPHdependentenzymes that cause cell death[1].

CUONPs once penetrated the cell membrane and entered inside the cell; they attacked mitochondria and caused mitochondrial disruption that caused an increase in oxidative stress. Stressed mitochondria were the main source of ROS because of electron transport chain (ETC) through which adenosine triphosphate (ATP) was generated. [48].

Several studies explained the resulting cytotoxicity due to the initial induction of lipid peroxidation of the membrane of mitochondria, which cause decoupling of oxidative phosphorylation; break down of electron transport and a decrease in mitochondrial membrane potential [49].

Under normal physiological conditions, cells had developed very complicate enzymatic and non-enzymatic antioxidant systems, working synergistically with each other scavenging the free radicals to protect against over production of reactive oxygen species (ROS). When generation of oxygen free radicals increased, they generated toxic intermediates that are usually responsible for oxidative stress due to imbalance between the level of ROS and antioxidants that detoxify toxic intermediates and restore damages [50].

Defense systems of Body collapsed to counterbalance oxidative stress and lead to the malfunctioning of biomolecules, change in the level of antioxidant enzymes, depletion of glutathione and perturbation of mitochondria. Damages also occurred in DNA and consequently cell death happened [51].

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Increased level of ROS induced a serious pathway that in turn activate the transcription of several genes; those genes change the regulatory pathways of the cell survival and eventually lead to apoptosis [52].

**An et al**. [53] indicate that oxidative damage was proposed as a main mechanism of cell damage induced by CUONPs. The Reactive Oxygen Species (ROS) released by CUONPs induce oxidative stress in the cells and the cells respond to this oxidative burden by fortifying their antioxidant defense mechanism to protect themselves. If this mechanism fails, oxidative damage occurs. These damage result in depletion of GPx and a significant increase in MDA levels. They suggest that CUONPs affect the oxidation –antioxidation homeostasis by increasing ROS and reducing antioxidant enzymes.

CUONPs interact with the acidic environment of the oxidative organelles (lysosomes and mitochondria) leading to ROS induction that become a persuasive mechanism behind toxicity associated with CUONPs. The CUONPs act as a pro-oxidant, i.e. they encourage oxidative stress or impeding antioxidants [28].

ROS generation leads to different biological responses that depends on the abundancy of biochemical factor (ROS), type of cellular pathways and the antioxidant response elements that are involved in oxidative stress. These responses include mitochondrial respiration, triggering NADPH dependent enzyme systems, inflammatory responses and damages cell membrane, DNA and Proteins ROS include hydrogen peroxide, anionic superoxide and hydroxyl free radical. Among ROS species, the hydroxyl (OH) toxic effect is considered as the most lethal one [54].

**Neurotoxicity of copper oxide nanoparticles**

Copper is an important requirement for stimulation of the production of several neurotransmitters in the brain like epinephrine and norepinephrine and can be found there in high levels. Copper tends to accumulate in different body tissues and organs including the brain. When taken in excess as dietary supplement, it may cause some neurotoxicity. Alzheimer's disease, a chronic neurodegenerative disorder and frequent cause of dementia, may also be associated with significant changes of copper levels in different brain tissues [55].

Nanoparticles are capable to enter the brain via direct way by translocation over the nerve ending of the olfactory bulb or indirect way through its uptake into the blood stream and crossing the blood brain barrier (BBB) [56]. (figure 4)

In recent years, extensive researches have been subjected towards the potential neurotoxicity of copper oxide nanoparticles. Because of the Nano-size of the CUONPs, they are able to passing through the BBB causing a threat to the central nervous system. Once they introduced to the blood stream, they result in BBB dysfunction, neuronal degeneration and swelling of astrocytes [56].

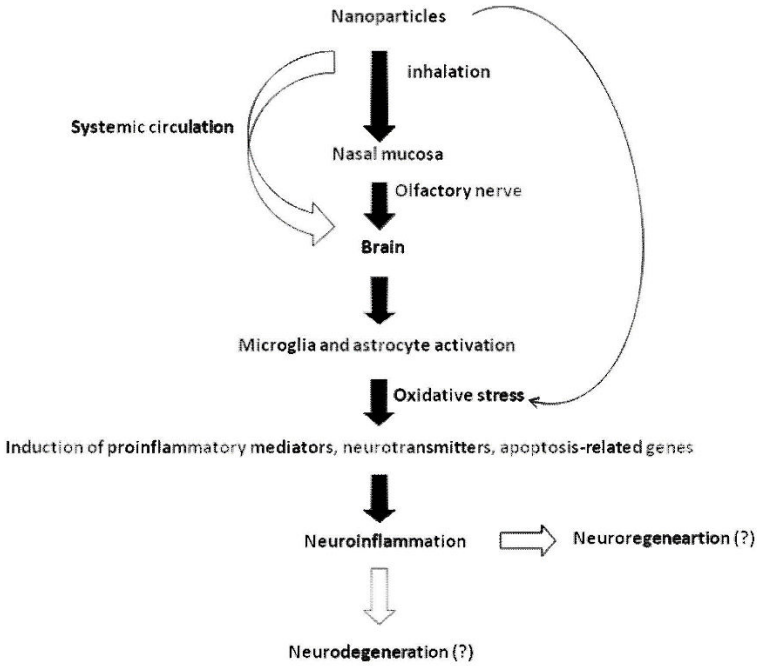


**Fig. 4**. Potential pathways of nanoparticles-induced neurotoxicity [58].

The mechanisms by which nanoparticles penetrate the BBB are still unclear. It appears that depending on the characteristics of nanoparticles they can produce cellular and oxidative stress within the microvessels of the

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brain. This cellular and oxidative stress result in releasing of different neurochemicals, cytokines and other neurodestructive factors such as lipid peroxidation, free radicals and nitric oxide. These neurodestructive factors also act on the cerebral microvessels and cause disruption of the permeability of the endothelial cell membrane allowing intravascular tracers to leak within the brain microfluid environment [59].

Breakdown of the BBB to protein tracers leads to vasogenic edema formation and subsequent brain damage. Passage of these restricted substances into the microfluid environment of the brain will thus initiate serious immunological, biochemical, cellular and molecular stress leading to serious injury in nerve cell, glial cell and myelin. Exposure of these cells to exogenous serum elements result in cell reactions in the brain [60].

Exposure to CUONPs produce cellular proliferation and release proinflammatory mediators, which affect the brain microvessel endothelial cells. They also increase prostaglandin E2 production and the extracellular levels of TNF-a and IL-1b. This result in the disruption of cerebral microvasculature by increasing its permeability [61].

It is possible that CUONPs can induce the programmed cell death by altering antioxidant mechanisms, and or increasing the level of oxidative stress. Exposure to CUONPs may up-regulate certain pro-apoptotic genes such as Bax, and down-regulate genes involved in apoptosis prevention such as Bcl-2. This change in gene expression may be followed with the decreased activity of several important detoxification enzymes such as glutathione S-tranferase and superoxide dismutase [50].

**Conclusion**

CUONPsimplies as an important type of nanoparticles because their wide rage of applications (industrial, electrical and medicinal). They have potential risks to the human and the surrounding environment. In this review, an overview of synthesis, properties, applications, route of exposure and toxicity of CUONPs are discussed. The objective is to focus on the mechanism of toxicity of CUONPs specially their neurotoxicity. More researches are needed to focus on nanoparticles and how to weaken their hazardous effects on the humans and the environment.

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