Toxicity of Copper Oxide Nanoparticles: A Review

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Abstract- Among the various nanoparticles, CuO nanoparticles (NPs) have earned significant attention of many researchers across the world due to their distinctive and unique characteristics, including small particle size, high surface area, reactivity, catalytic capabilities, and high surface to volume ratio. These characteristics have led to the usage of CuONPs in a wide range of commercial, industrial, and biological domains, including gas sensors, electrical materials, surfactants, antimicrobials and many more. However, prolonged usage of CuONPs has increased human exposure to these particles, raising the possibility of toxicity-related risks.

This review paper mainly focuses on the study of toxicological effects of copper oxide nanoparticles, with particular attention paid to *in-vitro* and *in-vivo* studies on a variety of cells and species, including humans, fish, rats, bacteria, and algae. Even the literature review mentioned the cytotoxic effect on human cells, including skin, lung, kidney and hepatic cells. The cytotoxic action of CuONPs depends on the production of reactive oxygen species, oxidative stress, lipid peroxidation, result in inflammation, genotoxicity, immunotoxicity, neurotoxicity etc.

Keywords– Cytotoxicity, reactive oxygen species, antimicrobial, ecological

1. INTRODUCTION

Nanomaterials differ from their macro counterparts because of their specific surface properties and reactivity. As nanomaterials have a higher surface to volume ratio and a large number of active sites on their surface, they are not only highly reactive but also hazardous in nature. Alongwith the study of applications of nanomaterials in the fields of health, material, reaction, catalysis, etc., their toxic consequences have also been concurrently investigated now-a-days.

CuONPs have found application in the fields of physics, chemistry and biology in heat transfer, photovoltaic cells, catalysis, and as bactericidal agents etc. Additionally, the antifungal activity of CuONPs has been documented in coating agents for textiles, plastics, etc [1].

Human body needs the trace amount of copper to maintain homeostasis but consumption of too much copper can result in jaundice, hemolysis, and even death. Intake of copper in high concentration can also lead to problems with the skin, respiratory and digestive systems. The toxicity of these materials has become increasingly important to investigate because of the negative impacts linked to CuONPs.

2. CLASSIFICATION AND SYNTHESIS OF Cu NANOMATERIALS

On the basis of chemical nature, Copper nanomaterials can be broadly categorized into copper nanoparticles and copper nanocompounds as shown in Fig.1. CuNPs can be further divided into

i) Cu+Metal (Fe, Ti, Zn),
ii) Cu and
iii) CuO,

whereas Cu nanocompounds may be further classified as:

1) Organic-inorganic (Polymers-NPs such as tubes, clusters, qdots, oxides etc.)
2) Metal-inorganic
3) Metal-organic

In an another classification, on the basis of dimensional structure as:

1) Zero - Cu^0, qdots, clusters
2) 1 D- nanotubes, nanopolymeric fibres
3) 2 D- nanocoating, polymeric films
4) 3D- polycrystals, nanostructures

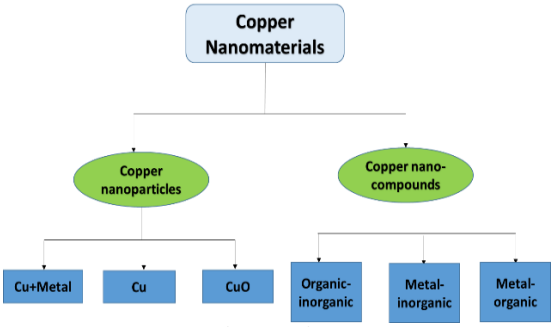

Figure 1: Classification of CuNanomaterials

Several chemical and green methods have been investigated for the synthesis of CuONPs. Chemical methods include, Wet-precipitation, Reduction-chemical and Elctrochemical methods. In chemical methods various Cu materials are taken as precursors, such as Cu(II), $CuSO_4$, $CuCl_2$, $Cu(NO3)_2$ and copper acetate Biosynthesized method include plant extracts and fungi as starting materials and the products obtained are proved to be better antimicrobial agent then that of obtained from chemical methods.

3. APPLICATIONS OF CuONPs

CuONPs are used as catalysts in a variety of organic processes. Alongwith, these are also found to exhibit significant antibacterial properties against a variety of bacterial strains such as *B. cereus, S. aureus* and *E. coli*. Moreover, these are also used for the treatment of drinking and waste water. In a recent research, Cu-Au microstructures are produced and claimed to be biosensors [3]. A two-dimensional nano sheet with MOF was also created [4] which is known to be utilized for the removal of impurities, particularly to immobilize uranium (VI) from the nuclear industry. CuNPs that have been biosynthesized from plant extract have been discovered to exhibit antibacterial, anti-inflammatory, antioxidant, and dye-removal properties [5].

4. TOXICITY OF CuONPs

Toxicity of CuONPs have been investigated in three broad areas such as genotoxicity, cytotoxicity and immunotoxicity. These toxic areas are influenced by numerous factors such as size, chemical behavior, composition, surface structure, morphology etc. The toxicity of nanoparticles depends on their release into the environment as metal cations [6]. While studying the toxicity, several factors are kept in mind such as surface chemistry, route of exposure, interaction with biological cells and nanoparticle binding.

4.1 Morphology, dissolution and dose of nanoparticles

The surface to volume ratio rises with decreasing nanoparticle size. The primary factor that determines the tocity or reactivity of any nanoparticle is its size. Several observations have proved that the particles larger than 100 nm can pass through a cell membrane and enter the cell, while particles smaller than 40 nm can even reach blood cells. The smaller particles are more harmful to cells than the larger ones [7]. Cell gets damaged when copper nanoparticles translocate across cells and pass through cell membranes [8]. CuONPs have been synthesized using a variety of techniques, including hydrothermal, chemical reduction, electro-chemical, sol-gel, and ultrasonic processes which lead to the formation of nanoparticles with different sizes. Vapour deposition method has been shown to yield NPs with a size of 33 nm, CuONPs synthesized by chemical reduction method [9] have lesser sizes as tiny as 45 nm, which can easily penetrate the cell. The literature also reports on several biological techniques [10] for the synthesis of CuONPs, and it is discovered that these techniques have exceptional efficacy in industrial, medical and environmental domains. Strong surface activity of CuONPs has been shown to make them active against a variety of fields. The result is in line with the idea that reactive oxygen species would be produced at higher surface areas. Due to their increased surface area, nanoparticles dissolve more readily in solvent molecules, react more readily and get assimilated easily, which has a hazardous effect. CuONPs cause the biological system to be toxically exposed to Cu ions in solution. Cu^{2+} ions concentrate in lysosomes following its release and exhibit cytotoxicity [11]. An another important factor which contribute to toxicity is the dose of NPs. It has also been observed that the toxicity of the nanoparticles against different cell structures increases many-fold with increasing dose. The survival of human lung epithelial cells was impacted by exposure to CuONPs at concentrations of 10, 25, and 50 µg/mL in 75, 66, and 48% of cases, respectively [12]. Following their release, NPs interact with soil, air, and water in the environment. This causes aggregation due to their surface characteristics, which then influences cellular absorption and ultimately results in toxicity.

4.2 Exposure path for copper nano particles

As seen in **Fig. 2**, the NPs enter the body through the respiratory, gastrointestinal, and skin. They then travel via the blood circulatory system to

various body sites, where they accumulate and cause damage or toxicity.

4.2.1 Inhalation

CuNPs are released into the air during the manufacture of rubber and asphalt [13], which the workers then breathe in. When NPs are inhaled, the biological system is impacted by several parameters including concentration, deposition, size, and presence in cells. Particle size and disposition in the lungs are inversely correlated. When NPs interact with epithelial cells in the lungs, inflammation results. NPs enter the central nervous system through the olfactory bulb [14]. The production of reactive oxygen species and inflammation results in the lungs.

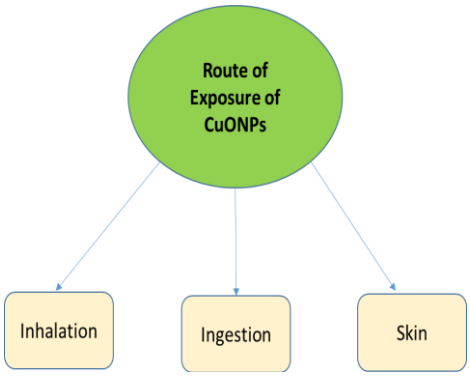

Figure 2: Exposure route of CuONPs

4.2.2 Ingestion

The most common way for nanoparticles to get into the gastrointestinal path is through diet and medicines. The absorption or assimilation of nanoparticles depends on surface area, shape, size, charge and bonding with other surface. When NPs enter in the gastrointestinal tract, they may possibly result in obstruction and even death. In addition to the gastrointestinal tract, NPs can also accumulate in the liver, heart, brain, and other organs. Fibrosis is caused by the accumulation of NPs in the hepatic system. The gastrointestinal tract is impacted by NPs in a number of ways such as development of ulcers, changes in nutrient absorption and persistent bleeding. Several experimental studies have proved the intake of CuNPs into body via breathing or food, water, drugs and translocation into various organs as the particles react with acid in stomach and get absorbed via villi in intestine [15].

4.2.3 External surface or via skin

No foreign particle can penetrate human skin and enter the body. However, NPs may enter the skin after it has been injured or the protective layer is removed potentially causing irritation, allergies or even the start of ROS production. It has been found through experimentation that nanoparticles are more harmful than their micro counter particles. They adhere to the body, react with acid, and enter the bloodstream as copper ions. Reports showed that CuONPs in the epidermis caused necrosis and cytokine releases.

4.3 In-Vitro Toxicity of CuONPs

4.3.1 Oxidative Stress and Reactive Oxygen Species

ROS stands for reactive oxygen spp., like O^{2-}, H_2O_2, and $\cdot OH$. Proteins, lipids and DNA are among the biological components that are quickly oxidized by these reactive species. The body possesses its own defense system. Various antioxidative enzymes and non-enzymatic substances including ascorbic acid, glutathione, peroxidases and catalase mitigate the negative effects of ROS. Oxidative stress is brought on via various hazardous intermediates that are created when the concentration of ROS is raised in the body. When the body's defense system is unable to control oxidative stress, glutathione is degraded, antioxidant molecule concentrations shift and biomolecules become aberrant. These events might potentially alter cell DNA and even result in cell death. Numerous empirical and literary investigations have validated these phenomena.

- There have also been reports of lipid peroxidation when CuONPs [16] come in contact with with *C. reinharatii*. CuONP cytotoxicity has been documented in cat fish liver cells [17].
- CuONPs have also been shown to exhibit cytotoxic behavior in human lung epithelial, cardiovascular endothelial, kidney and brain cells as well.
- The presence of CuONPs have also been investigated in A549 cells, which led to significant ROS content, high lipid peroxidation and low GSH levels. Lipid peroxidation is represented by an increase in MDA levels due to decreased GSH concentration. The results were in line with the fact that oxidative stress is the primary cause of cytotoxicity.
- CuONPs also changes the concentration of antioxidant enzymes such as GSH, CAT and SOD. As per experimental findings, on the decline of these enzymes, there occurs oxidative degradation in the embryo that lead to change in animal physiology. For

example, hatching issues in zebrafish have been noted [18].

- Another rat experiment supported the finding that exposure to CuONPs causes a decrease in the concentrations of the antioxidant enzymes CAT, TAC, and GSH and an increase in the concentration of nitric oxide [19].
- Fehmy and his colleagues [20] discovered that when CuONPs were exposed to GR, its antioxidative property was essentially inhibited upto 29–30%. The ratio of oxidized glutathione to total glutathione increased by 150% when CuONPs were present, indicating that the epithelial cells were able to stop CuONPs from producing reactive oxygen species. Overall, the result is the emergence of oxidative stress, which damages and sometimes even kills the cell.
- An experimental investigation using CuONP exposure on HBEC and A549 cells show a significant increase in the concentration of ROS. It has been observed that in the cells such as HL60, laryngeal and alveolar type-I epithelial cell, there was found higher level of ROS because of the cytotoxic behaviour of the CuONPs. There was also found depletion in NPSH and PSH concentration in liver and kidney cells. The above information represents that CuONPs weaken antioxidant system of different cell lines. Lipid peroxidation in these cells is supported by the higher concentration of MDA. CuONP exposure causes cytotoxicity because ROS-induced oxidative stress leads to genotoxicity.

4.3.2 Genotoxicity

Genotoxicity is the term used to describe chromosomal disruption, DNA damage and breakdown caused by mutagens that induce mutation. The main cause of DNA damage is through ROS development. CuONPs are absorbed by cells through endocytosis, which is where ROS are created. Apoptosis, or cell death results from damage to the DNA. Since any alteration to a genetic structure has the potential to cause cancer, studying genotoxicity is very important.

There are two ways that nanomaterials can damage DNA.

- In the first, the nanomaterials mix with the DNA to cause damage. Here, NPs penetrate the nucleus and interact with DNA, or they disrupt transcription and replication during cell division or mitosis.
- Additionally, NPs induce oxidative stress, which in turn triggers DNA damage. In this instance, NPs interact with spindles and mitotic proteins to prevent antioxidant molecules from doing their jobs. Phagocytes are exposed to NPs, which causes ROS production. To cause genotoxicity, these stimulated phagocytes rupture in an oxidative manner [21].

Size, shape, surface chemistry, dissolving pattern, particle accumulation, absorbance, rate of mutation brought on by mutagens, are some of the parameters that affect nanomaterials-induced genotoxicity. CuONPs exhibit genotoxic behavior when they penetrate cell membranes and engage in a reaction with DNA, as described by Wang and colleagues.

Numerous pieces of data supporting CuONP genotoxicity have been published so far. The size, form, duration of exposure, and conc all these factors affect toxicity. When exposed, ROS are created, which cause oxidative stress, which is followed by DNA modification, cell damage, and cell death. The p53 and p38 proteins, which damage DNA are induced by ROS [22]. Inflammatory cytokines are also produced as a result of ROS generation.

Effects of CuONPs induced genotoxicity on various parts of humans can be summarised in Table 1.

Table 1: Effects of genotoxicity by CuONPs on human cells

Affected Part of the body	Size of nanoparticles (nm)	Effects
A549 cells	Less than 100	Damage to DNA, cyto and neurotoxicity
Pulmonary epithelial cells	50	DNA damage via lipid peroxidation, oxidative stress, cell death
Bronchial epithelial cells	20-200	Oxidative stress, cell death
Skin cells	50	Necrosis, DNA damage by oxidative stress
Airpath epithelial cells92	-	Inflammation, Deposition in lungs

4.4 In vivo toxicity of CuONPs

Numerous animal cells have been used to study the hazardous behavior of CuONPs. This section includes the results of various scientific researches conducted worldwide:

- According to a report, the influence on neurons leading to hippocampal impairment is associated with memory and learning [23]. A 14-day experimental research on rats exposed to CuONPs showed memory and learning deficits. The propensity of nanoparticles to breach the blood-brain barrier and damage the central nervous system justifies the existence of Cu in the hippocampal region of the memory. The presence of CuONPs causes breakdown of the antioxidant system, disruption of homeostasis, neuronal injury and an overall increase in neurotoxicity.
- The effect of 14 days of exposure to CuONPs on cognitive behavior of rats was noted [24]. The anomalous behavior was caused by the release of presynaptic glutamate, a neurotransmitter that is associated with cognitive deficit and the destruction of the post synaptic receptor.
- Sun and his colleagues noticed that when CuONPs [25] were exposed to zebra fish larvae, their pattern of movement changed. It was observed that the locomotive behavior, including its speed, angular speed and distance travelled changed significantly when the concentration of NPs was increased. The CNS and muscle system had not developed as much, which resulted in a reduction in locomotive abilities.
- The harmful characteristics of CuONPs were observed in an additional experimental investigation using the nematode *Caenorhabditis elegans*. $CuSO_4$ and CuONPs were introduced to the nematode strains. When compared to strains exposed to $CuSO_4$ [26], it was found that strains treated with CuONPs had a substantial impact on body length. Similarly, exposure to CuONPs rather than $CuSO_4$ had a significant impact on eating behavior and reproduction.

In vitro and in vivo toxicity can be represented in Fig. 3.

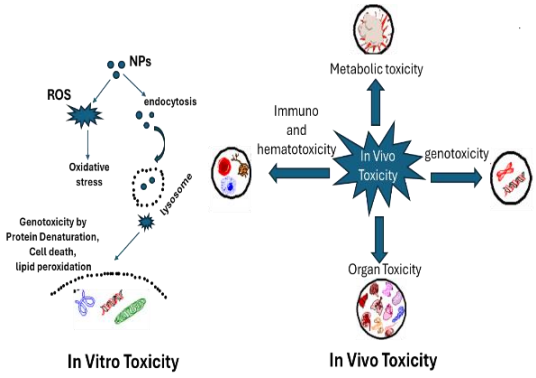

Figure 3: In-vitro and in-vivo toxicity of CuONPs

4.5 CuONPs induced Biochemical Changes

In an experimental research on rats, it was evidenced that exposure to CuONPs affects the nephrotic and hepatic organs, causing the kidney and liver to malfunction, respectively. Their physiological and biochemical roles are reflected in the effects. CuONP exposure increased the amount of ALT and ALP enzyme release on living membranes. When the dosage of CuONPs [27] was increased, Lee and his team also observed a rise in the levels of AST, ALP, CRE, and LDH and a decrease in the levels of total protein and triglyceride. Numerous investigators have documented an increase in liver enzymes, including AST, ALT, BUN, and CRE following CuONPs [28] intoxication. After administering a 1250 mg/kg conc. dose of CuONP to male rats, Wang and colleagues saw an increase in ALT, AST, LDH, and TCHO levels and a decrease in TG, sodium and chlorine [29]. Conversely, when the same concentration of CuONPs was administered to female rats, it was discovered that the levels of CPK and LDH [30] were elevated. Mice receiving CuONP intoxication also showed signs of significant inflammation, which is consistent with increased neutrophil counts. In a further investigation, Doudi et al. showed that on treating with CuONPs at doses of 10, 100, and 300 mg/kg [31], there was found effects on liver enzymes such as SGOT and SGPT. Meng and Cheng concluded in their separate research that because nano Cu particles had higher concentrations of TBA, ALP, and BUN [32] than macro and ionic copper, they are more hazardous.

4.6 Immunotoxicity of CuONPs

The immune system of the body functions by shielding the body against outside invaders, such as chemicals, microbes, and other elements that could disrupt homeostasis. Research on the application of nanotechnology in medicine is

being conducted by numerous scientists. There are four suggested mechanisms by which nanoparticles engage with immune cells: phagocytosis, endocytosis, inert uptake and interaction-based uptake. NPs are taken up by phagosomes in the phagocytosis mechanism, after which lysosomal breakdown takes place. Metal ions are released and the Fenton reaction produces reactive oxygen species (ROS), which impair mitochondrial function. A lysosomal fusion with the endosome takes place during the endocytosis mechanism.

Bypassing the endocytic or phagocytic phase and directly interacting with cell surface receptors, the other route is passive absorption within the cell. This initiates many intracellular activities, including the lectin and MAPK pathway, TLRU cascade, and others. In addition to intracellular processes, a number of external outcomes are attained, such as cytokine release and exocytosis.

Studies on immunotoxicity in mice were dose-dependent. CuONPs were originally collected in immune system cells. A mass of macrophages was observed at the exposure site. The macrophages require NO free radicals in order to eliminate the foreign particles. In an experiment, these LRS-modified macrophages were exposed to varying NP concentrations to observe how it affected the production of NO. The creation of NO was found to be inhibited by CuONPs, although Si, Ti, and Al nanoparticles had no effect.

All of those findings supported the theory that CuONPs inhibit macrophage immunological response by interfering with arginase activity. When CuONPs are applied to human cells, ROS generation occurs, which kills lymphocytes [33]. Human lymphocytes were isolated, and when they were exposed to CuONPs *in vitro*, the cell viability decreased. The development of ROS, lipid peroxidation, shift in GSH concentration, and damage to mitochondria and lysosomes were also impacted. In a study, the impact of CuONPs on *Mus musculus* blood cells, RBCs, WBCs, and platelets was also noted. When the mouse was injected with a dose of CuONP, WBCs increased while RBCs and platelets decreased. According to a study, when CuONPs were exposed, phagocytosis inhibition, LPS-mediated NO production and a decrease in GSH [34] levels were all seen.

Additionally, an immunotoxic investigation was conducted on earthworm species using a variety of measures, including phagocytotic behavior, NO and superoxide ions, enzyme activity, and total proteins after exposure to 1000 mg/kg of CuONPs and CuSO4 for 14 days [35]. The findings showed that the total protein count had decreased. Earthworm populations that reside in soil containing CuONPs and $CuSO_4$ were found to have significantly decreased.

4.7 Haematological changes caused by CuONPs

The haematological investigations conducted on rats exposed to CuONPs revealed an increase in reticulocytes but a decrease in RBCs, hemoglobin, Fe, HCV, and MCV. There was a decrease in lymphocytes as well, which resulted in a weakened immune system overall. Because there was an increased concentration of neutrophils and monocytes, there was seen inflammation in the exposed organs. Researchers found that there was a decrease in RBC levels in another rodent trial, which led to anemia and lower levels of HCT, HB, MCV and WBC [36]. Fe absorption decreases as Cu concentration rises.

4.8 Urine chemistry changes caused by CuONPs

CuONPs affect urine chemistry in addition to their effects on the liver and hematopoiesis. In a rat study, higher levels of glucose, AA, acetate, lactate, and TAMO were identified in the urine after CuONPs were administered, but lower levels of creatinine were noted. A spike in WBCs, ketone bodies and protein was detected in the urine test. Meng and colleagues [32] documented test findings for serum copper (SC) and urine copper (UC) in mice exposed to micro, nano and ionic Cu for 24 and 72 hours. When compared to other Cu kinds that broke down after 72 hours, the amount of SC was higher even after 72 hours of nano Cu intoxication**.**

4.9 Histological changes caused by CuONPs

Numerous studies have thoroughly documented and validated the study of CuONPs on a variety of organs. Doudi's research on rats revealed that during CuONPs poisoning, abnormalities were seen in the cells of the liver and lungs [31]. Even a reduced dosage may have an impact on the growth of fibrous tissues of lungs, loss of hexagonal lobes, and appearance of the central vein vasculature in live. The effects of CuONP doses of 100 and 200 mg/kg on the liver and kidney of rats were investigated. The rat liver was necrosed by the high dose (200 mg/kg). There was also evidence of necrosis in the proximal renal tube of the kidney and the proximal tubule showed signs of inflammation after receiving 100 mg/kg of treatment.

Wang and his colleagues [29] conducted separate studies on male and female rats, giving the latter a high dose of CuONPs. Both of the livers showed signs of cell inflammation and sinusoidal

dilatation. The same findings were noted after receiving Cu ions. On the other hand, when kidney cells were exposed to CuONPs rather than Cu ions, more abnormalities were seen, such as tubular dilatation and glomerular atrophy.

Lee and colleagues examined the effects of nano Cu and micro Cu [27] on several organs, including the spleen, thymus, liver, and kidney and found that nano Cu was more hazardous than micro Cu when compared to CuONPs combined with quercetin. Atrophic white pulp, yellowing splenic cells, distinct cortex and medulla and other symptoms like damaged cells, tubule dilatation and liver sinusoidal hepatic tissue dilation were observed.

A number of anomalies in renal tissues, including glomerulus inflammation and Bowman's capsule lumen deterioration were also noted by Meng and his colleagues.

Male and female rats were used in a comparative investigation to examine the effects of micro and nano Cu. It was shown that the former only had an effect on the rats at greater concentrations up to 5000 mg/kg, while the latter might harm organs even at lower concentrations [37]. Additionally, the impact of nano Cu on different organs varied in dose. Nano Cu produced glomerulonephritis and glomerulus inflammation at lower doses. The epithelial cells of proximal convoluted tubules were observed to be degrading at a medium dose, whereas necrobiosis was observed at a greater level. Purple deposits were observed in the protein fluid and the nucleus of the epithelial cells of the renal tubes and the renal tissues vanished entirely. Table 2 represents the histological effects of CuONPs on rats at different concentrations.

Table 4: CuONPs induced histological alterations in rats

Concentration mg/kg	Effects
10, 100, 300	Loss of hexagonal lobes in liver, increase fibrous structure in lungs
100, 200	Necrosis in hepatic tissues, necrosis and swelling in proximal renal tubes
1250-2500	Dilation of sinusoidal vacuoles in liver, decrease in white pulp in spleen cells, glomerulus atrophy
50, 100, 200	Necrosis in proximal renal tubes, inflammation in glomerulus, damage to Bowman's capsule
CuONPs with quercetin	Binucleated hepatocytes, sinusoidal dilation in liver
CuONPs with thiamine	Affected ovary by damaging corpus luteum

5. TOXICITY MECHANISM OF CuONPs

There are two proposed ways to explain the toxic mechanism of CuONPs: in one method, CuONPs cause the production of ROS and also trigger the redox process in cells, which in turn causes the production of ROS. When CuONPs enter the body through the skin, respiratory system or gastrointestinal tract, they mostly interact with the lysosome and mitochondria of any cell to produce reactive oxygen species (ROS), which causes cytotoxicity [38]. Numerous biochemical, morphological and physiological changes are brought about by the production of ROS. CuONPs cause oxidative stress by producing reactive oxygen species, which include super-oxides, H_2O_2, and $^{\cdot}OH$. Among them, free radicals or $^{\cdot}OH$, are said to be the most harmful. Because they can effectively damage DNA, cells and protein structures. It breaks down DNA strands, causes spontaneous cell deaths in various systemsand reduces disulphide bonds in proteins result is the abnormal unfold and refold of protein chains causes cancer and neurological pathologies. ROS also activates NADPH-dependent enzyme [39] and mitochondrial respiration. In addition, ROS can cause cell inflammation and damage to proteins, nuclear proteins and cell membranes. CuONPs cause DNA damage, mitochondrial damage and ultimately cell death when they are taken up by the cells by endocytosis. CuONPs also cause these NPs to trigger redox mechanisms in cells, particularly in the lungs, where NADPH oxidase enzyme is used by alveolar macrophages and neutrophils to act as ROS stimulators. This leads to the production of radicals that oxidize long-chain biomolecules, which causes oxidative stress and eventually, cell death.

Another mechanism for mitochondrial damage has been proposed. It involves the depolarization of the mitochondrial membrane upon exposure to CuONPs, which triggers NADPH-dependent enzymes that cause cell death. Numerous other effects of oxidative stress have been documented, including the solubility of Ca^{2+} ions, which degrades mitochondria and eventually results in cell death [40]. In addition, oxidative stress

causes disorders linked to aging, immunity heart and lungs.

5. CONCLUSION AND FUTURE SCOPE

CuONPs are one type of nanomaterial that has received particular interest due to its wide range of applications in many spheres of life. CuONPs are being used in more and more products, equipment, and medications, which is causing an increase in their discharge into the environment every day. Its hazardous effects on humans and environment are also noted, in addition to its uses. Human, environmental, and ecological health suffers as a result of its discharge. The main topics covered in this chapter were the benefits and drawbacks of CuONPs, the mechanism of intoxication, the effect of CuONPs on living cells through the generation of ROS, which causes oxidative stress and cell death, toxicological studies in the tissues of the lungs, stomach, liver, kidney, and heart, as well as in vitro and in vivo toxicology.

Many research projects were examined, and it was shown that exposure to different doses and times could have harmful effects. The nano size, shape, surface chemistry, and dose concentration of CuONPs determine their harmful effects. A few safety precautions must be taken before using CuONPs for human wellbeing. Greener approaches should be used to produce non-toxic CuONPs. Such as extracts of Cotton-fabrics, *Euphorbia falcate*, Fe_3O_4-Chitosan and *Cynomorium coccineum* have been investigated to be the ecofriendly methods of CuONPs synthesis. Further studies in this area are required to decrease toxicity while simultaneously boosting cell viability.

Its decomposition and disposal mechanisms are still unclear. Researchers are looking for low-cost, environmentally benign ways to synthesize CuONPs that also have very few negative environmental responses. The CuONPs monitoring system is still in its early stages of development. It is necessary to assess the detrimental impacts on CuONPs prior to their discharge into the environment. This can be accomplished by changing the exposure route, surface, size, dissolving factor and ROS generation, among other things. Even though there are many examples of safer CuONP usage in the literature, much more study is still needed to create a product that is affordable, safe, and efficient.

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