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REVIEW ARTICLE

Balancing the Essentiality and Genotoxicity of Copper: A Review

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ABSTRACT: Copper is an indispensable trace element necessary for the survival and proper functioning of nearly all living organisms, including humans. It plays a pivotal role in key physiological and biochemical processes, including energy production, iron metabolism, collagen synthesis, and neurotransmitter production. The distribution of copper and its transport proteins in the brain is crucial for maintaining cellular functions. However, disturbances in copper homeostasis can lead to severe neurological disorders and various health complications. This review delves into copper's dual role as both an essential nutrient and a toxic agent. Excess copper accumulation can induce oxidative stress, DNA damage, and genotoxicity, which are linked to its potential in causing chronic diseases. Special attention is given to copper nanoparticles and copper-based anticancer drugs, exploring their promising therapeutic applications alongside their toxicological profiles. We also provide insights into the mechanisms underlying copper-induced genotoxicity and discuss regulatory challenges in copper metabolism. This comprehensive review offers a critical assessment of copper's multifaceted role, addressing its benefits, risks, and future research directions.

Keywords: Copper homeostasis, Genotoxicity, Copper nanoparticles, Copper metabolism

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1. INTRODUCTION

Copper (Cu) is a bio-essential trace metal that plays a critical role in the biochemical and physiological processes of all living organisms. It exists primarily in two oxidation states: oxidized Cu(II) and reduced Cu(I), both of which contribute to its broad functionality in biological systems [1]. Copper has been recognized for its therapeutic potential since ancient times, often being used in folk medicine in the form of bracelets and ointments to treat joint and muscle pain. As an essential element, copper is indispensable for survival, acting as a structural and catalytic cofactor in several enzymatic processes.

In living organisms, copper is vital for energy production, iron metabolism, connective tissue formation, neurotransmitter synthesis, and antioxidant defense. The concentration of free copper ions in biological systems is tightly regulated. For example, in yeast cells, free copper ions are estimated to be present at levels as low as 10^{-1} to 10^{13} M, and in human blood plasma, copper is similarly regulated at extremely low concentrations [2]. This regulation is critical because while copper is essential for life, an excess of free copper ions can lead to cytotoxicity, oxidative stress, and damage to cellular structures, including DNA, proteins, and lipids.

One of the key roles of copper is in maintaining cellular homeostasis, particularly within the brain. Copper is involved in processes that ensure proper neurological function, and any imbalance in copper homeostasis can have significant consequences [3]. For instance, copper deficiency can result in stunted growth, impaired immune function, and neurological disorders. Conversely, excessive copper accumulation can lead to conditions such as Wilson's disease and Alzheimer's disease [4]. These diseases are associated with abnormal copper metabolism, leading to toxic effects in various tissues, especially the liver and brain [3].

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The distribution of copper in the human body is carefully regulated, with the highest concentrations found in cerebrospinal fluid (approximately 5 µg/mL), followed by blood, plasma, and lymph (Table 1). The copper content in foods also varies widely; for instance, nuts, shellfish, and organic soils contain high levels of copper (12-37 µg/g), while in humans and animals, tissue copper levels are typically around 1.5-2.5 µg/g (Table 2). Organ meats, particularly the liver, are rich in copper, as are shellfish and seeds such as nuts and grains. In contrast, fruits and vegetables contain much lower concentrations of this essential trace element.

Copper enters the body primarily through the alimentary tract, with minimal absorption through the skin under normal conditions. However, when applied in high concentrations, such as in the form of ointments or copper bracelets, it can be absorbed transdermally. In plants, copper is absorbed through the roots, and to a lesser extent, through the leaves. Once absorbed, copper is transported throughout the body bound to various proteins that prevent free copper ions from causing cellular damage. In the bloodstream, copper is carried primarily by ceruloplasmin, a copper-binding protein that accounts for about 95% of the copper in human serum [5]. Ceruloplasmin is a glycosylated multi-copper ferroxidase that is synthesized in the liver. However, it is not part of the exchangeable copper pool and does not directly incorporate copper ions after entering the bloodstream. Instead, copper is added to ceruloplasmin during its synthesis in the liver. Other copper-binding proteins, such as albumin and transcuprein, are responsible for transporting copper in the bloodstream. Transcuprein has a higher affinity for Cu(II) than albumin and is the first to bind newly absorbed copper ions [1]. While copper is essential for many biological functions, its redox properties also make it potentially harmful when present in excess. Copper can catalyze the formation of highly reactive oxygen species (ROS), which can lead to oxidative damage. ROS are implicated in a variety of pathological conditions, including cancer, neurodegenerative diseases, and aging. The ability of copper to participate in redox reactions is both a blessing and a curse—it is essential for processes like mitochondrial respiration and antioxidant defense, but it also poses a risk for cellular damage through mechanisms such as lipid peroxidation, protein oxidation, and DNA cleavage [6].

Copper's redox properties also contribute to its antibacterial, antitumor, and antioxidant activities, making copper-based compounds attractive candidates for therapeutic applications. For example, copper complexes have been investigated for their potential in cancer treatment, where they exhibit selective toxicity toward cancer cells through the generation of ROS and disruption of cellular processes. Copper's role in wound healing and neurodegenerative disorders has also been explored, with studies suggesting that copper-based therapies may offer benefits in these areas by promoting tissue repair and reducing oxidative stress [7].

However, despite its essential role in biological systems, copper toxicity is a significant concern when its levels are not properly regulated. Excess copper can lead to conditions such as Wilson's disease, where copper accumulates in the liver and brain, causing liver failure, neurological damage, and psychiatric symptoms. Additionally, chronic exposure to high levels of copper has been linked to genotoxic effects, including DNA damage and chromosomal instability. Copper's ability to generate ROS and its involvement in oxidative stress are key mechanisms underlying its genotoxicity. These effects can contribute to the development of various diseases, including cancer, by inducing mutations, DNA breaks, and other genetic alterations [8-13]. Given the dual nature of copper as both an essential nutrient and a potential toxin, it is critical to maintain a balance in copper intake. While dietary copper is necessary for normal biological function, excessive intake or exposure can have detrimental effects.

Table 1. Distribution of copper in body fluids.

S. No.	Body fluids	Concentration (Cu) ($\mu g/ml$)
1.	**Blood**	
	Whole Blood	1.11
	Plasma	1.13
2.	Lymph	1.17
3.	Saliva	0.22
4.	Fallopian Secretions	1.1
5.	Pleural Fluid	0.6
6.	Aqueous humor	0.14
7.	Gastric Juice	0.4
8.	Pancreatic Juice	0.26
9.	Cerebrospinal Fluid	5
10.	Urine	0.05-0.4

Table 2. Distribution of copper content of food, water, soil and organisms.

S. No.	Foods	Content (microgram/gram)
1.	Muscle Meats	0.9-1
2.	Sea	2-3
3.	Freshwater	0.3-3
4.	Shell Fish	12-37
5.	Poultry	0.5-3
6.	Liver	4.5-6.2
7.	Nuts	6-37
8.	Grains and seeds	3-8
9.	Bran	15
10.	Vegetables	0.3-3
11.	Fruits	0.4-1.5
12.	Potatoes	2.1
13.	Soils (Organic)	20-30
14.	Soils (Inorganic)	>_4
15.	Animals	1.5-2.5
16.	Humans	1.7

The recommended daily allowance (RDA) for copper in adults is approximately 900 micrograms per day, with higher levels recommended for pregnant and lactating women. However, individuals should be cautious of excessive copper exposure, particularly in occupational settings where copper dust or fumes may be present [14-19]. Copper is an essential trace element that plays a vital role in numerous physiological processes, but it also poses a risk of toxicity when present in excess [20].

This review aims to provide a comprehensive analysis of copper's essentiality and genotoxicity, exploring the mechanisms through which copper contributes to both health and disease. In particular, the review will focus on the emerging role of copper nanoparticles and copper-based anticancer drugs, highlighting recent advances and ongoing challenges in harnessing copper's potential for therapeutic applications.

2. ABSORPTION OF COPPER

Copper is an essential trace element in mammals, involved in numerous physiological processes, including redox reactions, iron metabolism, and the function of enzymes like cytochrome c oxidase and superoxide dismutase. In mammals, the primary site for copper absorption is the small intestine, where absorption efficiency in humans averages between 55% to 75%. Notably, this absorption rate does not decline with aging [8]. In contrast, absorption rates in rats are lower, ranging between 30% to 40%. Copper absorption in the intestinal mucosa occurs through brush border cells. The absorbed copper is then transferred across the basolateral membrane into the interstitial fluid and bloodstream via different mechanisms.

Copper's entry into the intestinal mucosa involves a non-energy-dependent diffusion process across the mucosal barrier. This passive process contrasts with the energy-dependent transfer of copper across the basolateral membrane, which appears to be the rate-limiting step of absorption. Specific transport proteins, including P-type ATPases, facilitate this energy-dependent process. These ATPases contain methionine and cysteine motifs, which are believed to be crucial for the binding and transport of Cu(II) ions [9]. Copper absorption is finely regulated based on the body's needs, a mechanism that helps maintain homeostasis. Studies in rats have shown that copper absorption adjusts to the dietary intake level: when intake is low, the body absorbs a higher proportion of available copper, whereas at higher intakes, absorption decreases. This adaptive mechanism helps prevent copper deficiency when dietary intake is low and copper toxicity when intake is excessive [9]. This regulation is observed over periods of days to weeks, ensuring that copper levels are maintained within a narrow, healthy range. In humans, the recommended dietary intake for copper ranges from 1.5 to 3.0 mg per day for adults. This intake range is considered both safe and sufficient to meet physiological needs [10]. However, research by Turnlund has shown that even lower intakes, such as 0.8 mg per day, are sufficient to maintain body copper status for periods of up to 42 days [11]. This finding suggests that the actual requirement for copper may be lower than the recommended 1.5 mg/day. The process of copper entering cells through endocytosis and the pathways responsible for the generation of reactive oxygen species (ROS), which can lead to cellular damage and death if not properly regulated. Once absorbed,

copper is transported through the bloodstream, initially binding to two major proteins: albumin and transcuprein. These proteins play essential roles in copper transport, with the majority of the absorbed copper ultimately being deposited in the liver [12, 13]. Albumin is the principal copper-binding protein in plasma, where it binds ionic copper (Cu(II)) with high affinity at its amino terminus. Human plasma albumin can accommodate up to approximately 40 mg of copper per liter [13].

Copper distribution within the body follows a two-phase process. In the first phase, copper is taken up by the liver and kidneys, primarily through binding to transcuprein. In the second phase, copper is distributed to other tissues, with ceruloplasmin acting as the primary transporter [13]. While ceruloplasmin is crucial for copper transport to tissues, the exact mechanisms by which copper is taken up by cells, particularly hepatocytes, are not fully understood. Some evidence suggests that metal ion transporter systems may facilitate the uptake of copper into cells, but further research is needed to clarify this process [14]. These systems might also play a role in the release of copper back into the plasma or in the transport of other metal ions, although this remains speculative.

Copper is also transported to the brain, where it plays a vital role in neuronal development, maturation, and function. The transport of copper into the brain occurs in a controlled manner through specialized transporters located at the brain's boundaries, such as the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCB). These barriers help regulate copper homeostasis in the brain by controlling its entry and exit.

One of the key transporters involved in copper's movement into the brain is the copper transporter 1 (CTR1), which facilitates the transfer of copper from the bloodstream across the endothelial cells that make up the BBB. Once copper crosses the BBB, it enters the brain parenchyma, where it is transported by the ATP7A protein. ATP7A plays a crucial role in maintaining proper copper levels within the brain. When copper levels are in excess, ATP7A helps release copper from brain cells into the cerebrospinal fluid (CSF). From the CSF, copper is taken up by cells of the blood-cerebrospinal fluid barrier (BCB), which either store the copper for later use or release it into the bloodstream through the action of the ATP7B protein [15] (Figure 1).

Several genetic mutations can disrupt copper metabolism, leading to severe disorders. One such disorder is Menkes disease, which results from mutations in the ATP7A gene. In Menkes disease, copper absorption and distribution are severely impaired. Affected individuals have abnormally low copper levels in the liver and brain, while copper levels are elevated in other tissues, such as the kidneys and intestinal lining. This imbalance leads to neurological symptoms, connective tissue abnormalities, and, if untreated, early death [15].

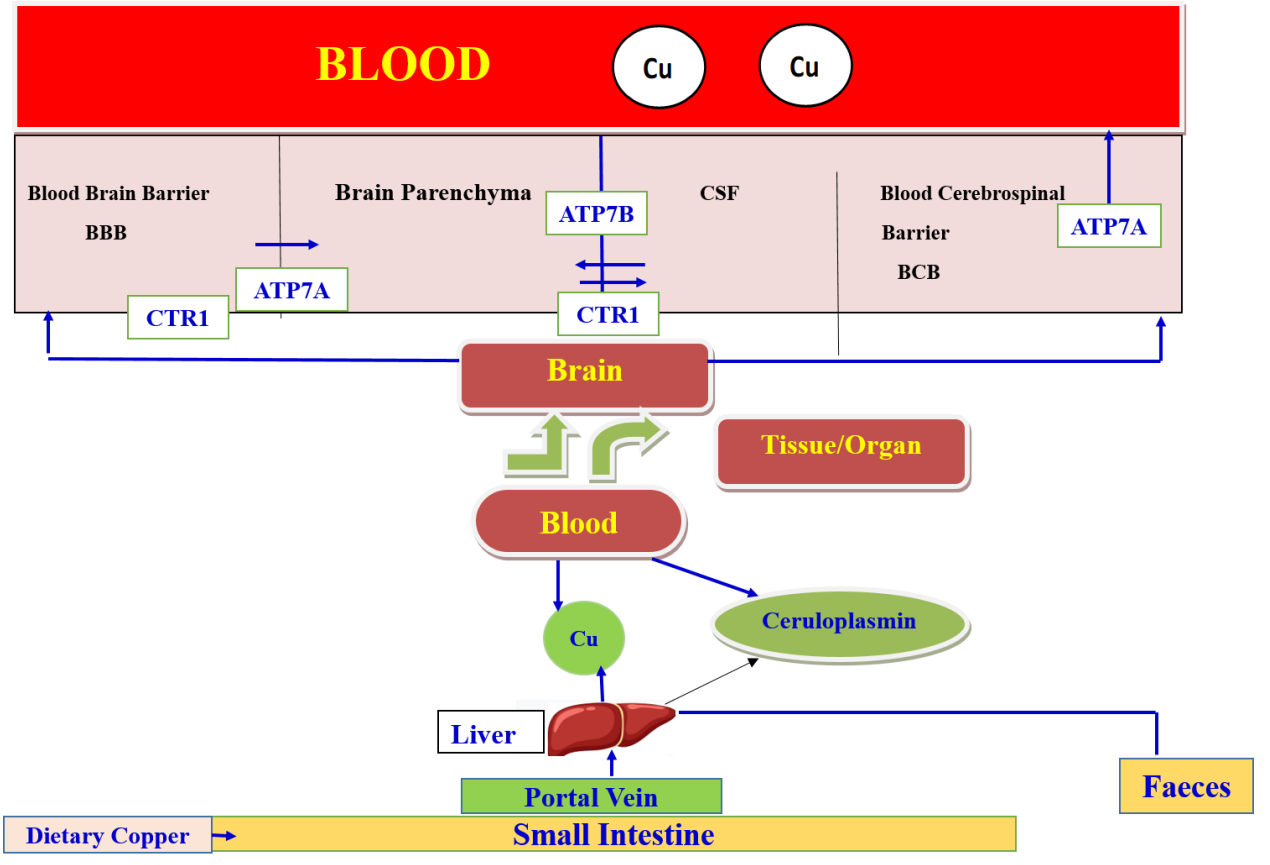

Fig. 1. Dietary absorption and transport of copper.

Menkes disease highlights the importance of ATP7A in copper transport and distribution, particularly in the brain. Without functional ATP7A, copper cannot be properly transported into the brain, leading to copper deficiency in this organ despite an overall excess of copper in the body. Another copper-related genetic disorder is Wilson's disease, which is caused by mutations in the ATP7B gene. ATP7B plays a critical role in copper excretion and the incorporation of copper into ceruloplasmin, the primary copper-transporting protein in the blood. In Wilson's disease, ATP7B mutations prevent the proper excretion of copper into bile and its incorporation into ceruloplasmin. As a result, copper accumulates in the liver, brain, and other organs, leading to liver disease, neurological symptoms, and psychiatric disturbances [15]. One of the key diagnostic markers for Wilson's disease is low serum ceruloplasmin levels. In affected individuals, ceruloplasmin levels are typically below 20 mg/dL, compared to the normal range of 20 to 40 mg/dL [16]. Early diagnosis and treatment of Wilson's disease are critical to prevent the progressive accumulation of copper in the liver and brain, which can lead to irreversible damage.

Although copper is essential for numerous physiological functions, maintaining copper homeostasis is critical, as both copper deficiency and copper toxicity can have severe consequences. The body's regulatory systems are finely tuned to maintain copper levels within a narrow range. Excess copper can generate reactive oxygen species (ROS), which can cause oxidative damage to cells and tissues if not properly controlled [16]. Under normal conditions, copper homeostasis is maintained through a balance of copper absorption, transport, and excretion. The liver plays a central role in regulating copper levels, storing excess copper and excreting it into bile for removal from the body. Ceruloplasmin and other copper-binding proteins help transport copper to tissues in need while preventing the accumulation of free copper ions, which can catalyze the production of ROS and lead to cellular damage [13]. Copper absorption, transport, and metabolism are tightly regulated processes that ensure adequate copper levels for physiological functions while preventing toxic accumulation. Genetic disorders like Menkes and Wilson's disease disrupt these regulatory systems, leading to copper imbalances that can cause severe health problems. Understanding the mechanisms of copper absorption and transport, particularly the role of key proteins like ATP7A and ATP7B, is critical for developing treatments for these disorders and managing copper-related diseases [9, 14, 15, 16].

3. METABOLISM OF COPPER

Copper is an essential trace element in the body, existing primarily in two ionic forms: cuprous (Cu^{+}) and cupric (Cu^{2+}). Cuprous copper (Cu^{+}) typically predominates in the extracellular oxidative environment. For copper to enter cells, it must be in the Cu^{+} form, a process facilitated by copper reductases. These enzymes, like those from the six transmembrane epithelial antigen of the prostate (STEAP) family, convert Cu^{2+} to Cu^{+}, ensuring its bioavailability. A recent study has identified a novel copper reductase enzyme—the histone H3-H4 tetramer—in the yeast *Saccharomyces cerevisiae*. This enzyme binds to Cu^{2+} and catalyzes its reduction to Cu^{+}, thus maintaining mitochondrial electron transport chain function [17].

Once inside cells, copper is rapidly shuttled to various organelles and proteins where it serves as a critical cofactor. In mammals, copper's primary functions are in energy metabolism, electron transport, and antioxidant defense, underscoring its indispensable role in life processes. Copper is initially absorbed in the stomach and duodenum in its cupric ion form (Cu^{2+}) and transported to the liver. There, it becomes integrated into ceruloplasmin, a copper-dependent protein responsible for copper transport throughout the body. Ceruloplasmin not only serves as a carrier but also plays a key role in the oxidation of iron, which is crucial for hemoglobin synthesis [18].

Apart from ceruloplasmin, copper is also associated with several other critical proteins, including cytochrome c oxidase, superoxide dismutase (SOD), and metallothionein. Cytochrome c oxidase is essential for cellular respiration and energy production, while SOD serves as a major antioxidant defense mechanism by scavenging superoxide radicals. Metallothionein, on the other hand, helps in copper homeostasis and detoxification of heavy metals. The fact that copper-dependent enzymes are so widespread and functionally diverse underscores the importance of this metal for fundamental biological processes.

Interestingly, the body's copper reserves are minimal, with most of the element actively engaged in metabolic processes or in transit to its sites of action. There is very little free copper in the blood, and the limited amount that may filter through the kidneys into the urine is typically reabsorbed, ensuring copper conservation. This controlled metabolism highlights the importance of maintaining copper balance, as both deficiency and excess can be detrimental. In humans, copper homeostasis is finely regulated, with the liver playing a central role in both copper storage and excretion. In cases of copper excess, the liver secretes the excess into bile for elimination. When copper balance is disrupted, serious health conditions can arise. For instance, in Wilson's disease, mutations in the ATP7B gene impede the excretion of copper into bile, leading to toxic copper accumulation, particularly in the liver and brain. Conversely, Menkes disease, caused by mutations in the ATP7A gene, leads to copper deficiency, as copper cannot be transported adequately from intestinal cells into the bloodstream [19, 20].

Copper metabolism is a finely regulated process that involves its reduction, transport, and use as a cofactor for critical enzymes. This balance ensures copper absorption, distribution, and excretion occur without reaching toxic levels. Copper supports essential biological functions, including energy production, antioxidant defense, and iron metabolism. Proper regulation prevents disorders like Wilson's disease, caused by copper accumulation, and Menkes disease, resulting from copper deficiency. Overall,

copper's tightly controlled metabolism underscores its importance as a trace element vital for maintaining health and physiological functions.

3. ESSENTIALITY OF COPPER

Copper is a trace element essential for numerous physiological functions in the human body. Its necessity is highlighted by various studies that reveal the adverse effects of copper deficiency. For instance, a study published in the Journal of Trace Elements in Medicine and Biology demonstrated that copper deficiency could lead to significant health issues such as anemia, neutropenia (a low white blood cell count), and bone abnormalities [18].

3.1. Medicinal Use of Copper

Furthermore, copper plays a pivotal role in maintaining cardiovascular health. Research published in the Journal of Nutrition illustrated that copper helps regulate blood pressure and prevent the development of cardiovascular diseases [19]. In addition to its role in hematologic and cardiovascular functions, copper is essential for the proper functioning of the nervous system. A study in Nature Communications demonstrated that copper deficiency could result in cognitive decline and is potentially linked to the onset of neurodegenerative diseases such as Alzheimer's [20]. These studies, along with others, underscore the critical nature of copper for overall health and well-being. Copper's ability to act as a cofactor for various enzymes involved in antioxidant defense, energy production, and connective tissue formation further solidifies its role as an indispensable element for human life. Copper has been used for medicinal purposes for thousands of years, particularly in traditional systems like Ayurvedic and Chinese medicine. Figure 2 highlights key medicinal uses of copper. Several modern scientific studies have validated the therapeutic potential of copper, some of which are discussed below:

3.1.1. Antimicrobial Properties

Copper exhibits potent antimicrobial properties, making it effective against a wide range of microorganisms, including bacteria, viruses, and fungi. Copper surfaces have been implemented in hospitals to reduce infection rates, especially in high-risk areas. Copper nanoparticles are being investigated for their potential as antimicrobial agents in wound healing and other medicinal applications. Studies have shown that copper's antimicrobial effect is largely due to its ability to disrupt microbial cell membranes, leading to cell death [21].

3.1.2. Anti-inflammatory Effects

Research has also demonstrated copper's anti-inflammatory properties. For instance, patients with rheumatoid arthritis have reported reduced pain and inflammation when using copper bracelets [22]. Although more research is needed to establish the exact mechanism, it is believed that copper may help modulate inflammatory pathways in the body, thus reducing chronic inflammation in conditions such as arthritis.

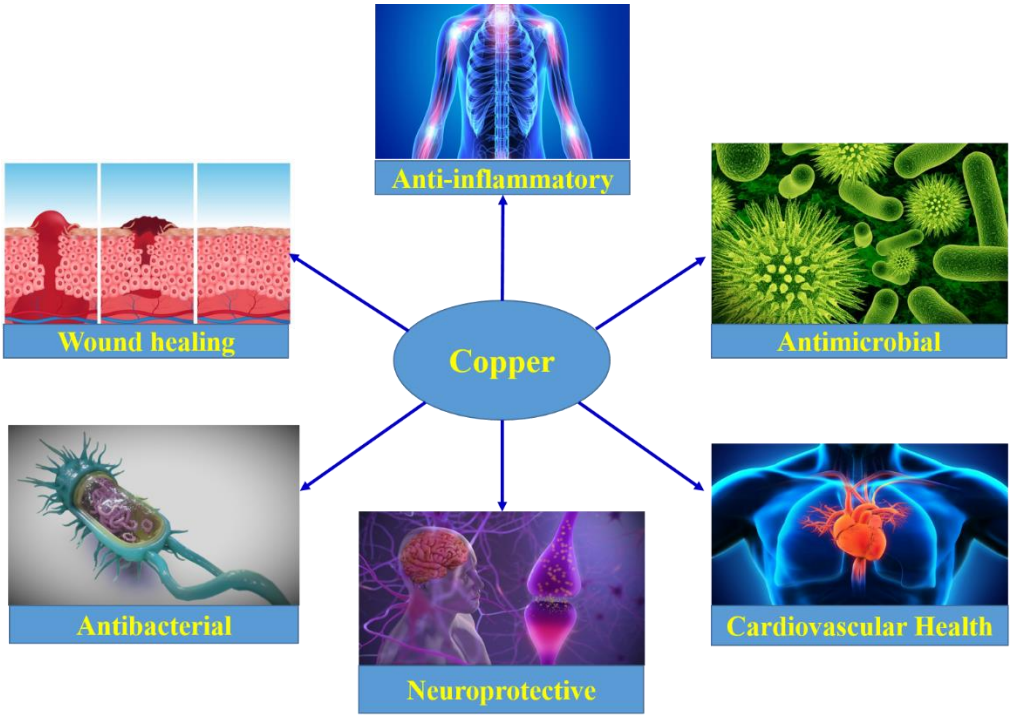

Fig. 2. Medicinal use of copper.

3.1.3. Wound Healing

Copper is essential for wound healing, primarily because it stimulates the production of collagen and other proteins crucial for tissue repair. Studies have shown that copper-containing dressings can accelerate wound healing, particularly in burn victims and patients with chronic wounds [23].

3.1.4. Antibacterial Agent

Copper's efficacy as an antibacterial agent has been well-documented, particularly when used in nanoparticle form. For instance, chitosan-copper nanoparticles have demonstrated strong antibacterial activity against various bacterial species, including MRSA, Bacillus subtilis, Pseudomonas aeruginosa, and Salmonella choleraesuis [24]. Copper nanoparticles (Cu-NPs) and cuprous oxide (Cu_2O) particles have been shown to degrade bacterial plasmid DNA in both Gram-positive and Gram-negative bacteria, in a dose-dependent manner [25, 26].

Studies have further revealed that the size of the copper nanoparticles is crucial for their antibacterial efficacy. Smaller particles (around 4.8 nm in size) exhibit better antimicrobial activity compared to larger particles [27, 28]. This enhanced activity is due to the smaller particles' greater ability to penetrate bacterial cells. However, it is important to note that copper nanoparticles can also exhibit cytotoxic and genotoxic effects due to their small size, which necessitates careful consideration before their application in medical treatments [29, 30].

3.1.5. Neuroprotective Effects

In neurodegenerative diseases such as Alzheimer's and Parkinson's, copper has demonstrated neuroprotective effects. In animal models, copper supplementation has been shown to protect nerve cells from damage [31]. Copper is crucial for maintaining the function of enzymes involved in antioxidant defense, which can help protect neurons from oxidative stress—a key factor in neurodegeneration.

3.1.6. Cardiovascular Health

Copper also plays a significant role in cardiovascular health, particularly in the formation and maintenance of blood vessels. Copper deficiency has been linked to various cardiovascular diseases, including hypertension and atherosclerosis [32]. Copper helps maintain the integrity of the blood vessels by facilitating the cross-linking of collagen and elastin, which are essential components of the vascular system.

3.2. Potential Anticancer Properties of Copper

Recent research has highlighted copper's potential role in cancer therapy. Evidence suggests that cancer cells exhibit a higher uptake of copper, which they acquire from ceruloplasmin and nonceruloplasmin fractions in the plasma [33]. Elevated copper levels have been observed in tumor cells, making copper a potential target for anticancer strategies.

3.2.1. Copper and Angiogenesis

Angiogenesis, the formation of new blood vessels, is crucial for tumor growth and metastasis. Copper has been shown to promote angiogenesis by enhancing the activity of angiogenic factors like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [34]. Inhibition of copper-dependent angiogenesis has emerged as a promising strategy for halting tumor growth. Copper chelation therapies, which reduce copper levels in the body, have demonstrated potential in inhibiting tumor angiogenesis and metastasis.

3.2.2. Copper-Induced Apoptosis

Apoptosis, or programmed cell death, is a process that is dysregulated in many cancer cells. Copper has been shown to induce apoptosis in cancer cells through the activation of the p53 tumor suppressor pathway [35]. The p53 protein is often referred to as the "guardian of the genome" because it plays a crucial role in preventing cancer development by promoting apoptosis in damaged or abnormal cells. Copper also inhibits anti-apoptotic proteins like Bcl-2 and Bcl-xl, further promoting cell death in cancerous tissues. Additionally, several copper-containing compounds, such as copper(II) complexes, have been shown to induce oxidative stress in cancer cells, leading to apoptosis. By selectively targeting cancer cells, copper-based therapies hold promise as a new avenue for cancer treatment. Copper is a vital trace element with diverse roles in human health. From its essentiality in maintaining cardiovascular, neurological, and immune function to its potential therapeutic applications, copper remains a key component of modern medicine. Studies have underscored copper's importance in preventing and treating a variety of health issues, from cardiovascular diseases to neurodegenerative disorders and cancer. However, copper's roles are not without complexity. While it offers numerous health benefits, both deficiency and excess can lead to severe consequences. The balance between copper's beneficial effects and potential toxicity highlights the need for further research to fully understand its metabolic pathways, mechanisms of action, and potential in therapeutic applications.

4. RECENT ADVANCES: COPPER NANOPARTICLES

Global research and development have led to a rapid advancement of nanotechnology, the scientific revolution of the twenty-first century. The production of matter at the

nanoscale has the greatest impact on the development of this field. The term "nanoparticle" refers to a particle with at least one dimension and a maximum size of 100 nm. Surface to volume ratios of nanoparticle is high. Existence of metal nanoparticle was given by Faraday. Due to quantum effects and their high surface-to-volume ratio, metal nanoparticles exhibit remarkable UV-visible sensitivity, electrical, catalytic, thermal, and antibacterial capabilities [36]. Because of the reduced particle size, there are many more atoms on the surface. The form, size, conductivity, and sensitivity to the ultraviolet and visible all affect the surface area to volume ratio of the particles. Because of their absorption sensitivity, electrical, medicinal, magnetic [37] and catalytic properties based on size, shape, and structure, metal nanoparticles are used in catalysis, sensing [38] and optoelectronics [39]. Copper nanoparticles have potential uses in optics, electronics, and medicine as well as in the production of lubricants, nanofluids, conductive films, and antibacterial agents. Due to their superior conductivity, copper nanoparticles are more significant than those of other, more stable metals. One of the most significant and beneficial metal nanoparticles is copper. For several processes, such as catalytic reduction, they are commonly utilized as catalysts. There have also been reports on copper nanoparticles' influence on fluorescent materials. Fluorescence quenching, dye aggregation, dye disaggregation, and fluorescence amplification may all be brought on by copper nanoparticles. According to studies conducted, this feature may be exploited for bio sensing and bio labeling. Drugs with copper as an ingredient are frequently used to weaken tumors and cancer cells. Since copper nanoparticle clusters form with a mutant form of human hemoglobin, they may be used as screening tools for hemoglobinopathies like b-thalassemia. Applications of copper nanoparticles for imaging and high antithrombic activity have been investigated. According to Hokita, these materials have also been employed in conducting applications [40].

5. GENOTOXICITY CAUSED BY COPPER

Excessive copper exposure can lead to genotoxicity, which refers to the damage to the genetic material, i.e., DNA, resulting in mutations, chromosomal aberrations, and cell death [41-52]. A measure of genotoxicity against any harmful chemical is the formation of micronuclei, the induction of chromosomal abnormalities, and the degree of damage to DNA [53, 54]. There are two ways that nanomaterial can affect DNA: directly by binding to DNA strands or indirectly by inducing oxidative stress in response to NP exposure. Direct genotoxicity occurs when NPs directly interact with DNA molecules during mitosis or when they enter the nucleus through nuclear pores. Through interactions with nuclear proteins, mitotic spindles, checkpoints, and the suppression of the antioxidant defense system, NPs cause harm during indirect genotoxicity (Figure 3). The Hodge and Sterner scale rates the toxicity of copper nanoparticles as class 3, moderately harmful. Copper nanoparticles have been shown to target the liver, kidneys, and spleen in particular in experimental mice [41]. Copper nanoparticles produced kidney and spleen discoloration and spleen atrophy at doses of 108–<1080 mg/kg and 25 nm particle size. A study conducted CuO nanoparticles in doses (<400ppm) is safe for biomedical application and has no side effects, but higher doses (>400ppm) is toxic [42]. One study investigated the genotoxic effects of copper in human lymphocytes and found that copper treatment resulted in DNA damage, chromosomal aberrations, and micronuclei formation. The researchers also observed an increase in oxidative stress markers and a decrease in antioxidant enzyme activities, indicating that copper- induced genotoxicity is associated with oxidative stress. Another study showed that copper exposure led to DNA damage and chromosomal aberrations in human peripheral blood lymphocytes. The researchers found that copper-induced genotoxicity was associated with the generation of ROS and activation of JNK and p38 MAPK signaling pathways. In a study on the genotoxic effects of copper nanoparticles, it was found that copper nanoparticles caused DNA damage and chromosomal aberrations in human lung fibroblasts.

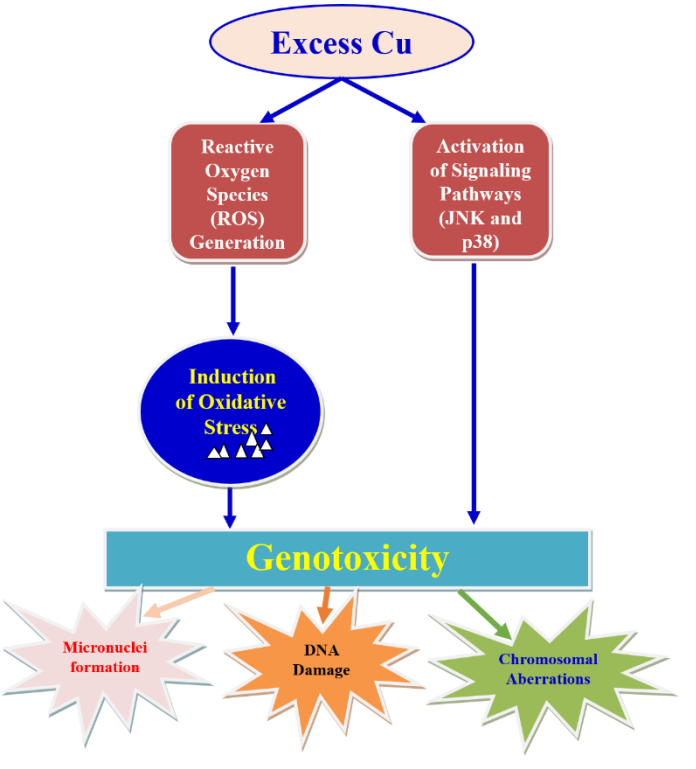

Fig. 3. Diagrammatic Representation of Copper Nanoparticles induced genotoxicity.

In addition to oxidative stress and the activation of signaling pathways, copper-induced genotoxicity can also occur via the formation of DNA- copper complexes. A study investigated the genotoxic effects of copper on DNA in vitro and found that copper can bind to DNA and cause structural changes,

resulting in DNA damage and mutations. Copper's ability to release ions leads to oxidative stress by generating Reactive Oxygen Species (ROS) in aerobic condition that also defines its antibacterial properties. Superoxide anions (O_2^-) hydrogen peroxide (H_2O_2) and the hydroxyl free radical (OH) make up the majority of ROS. Generation of ROS, which are highly reactive chemicals that can harm biological components, including DNA, proteins, and lipids. Additionally, it alters chromosomal stability and causes the production of micronuclei, which is a sign of genotoxicity [55]. Copper-released ions can enter the cell after cell membrane gets degraded. According to redox cycling between native Cu, Cu (I), and Cu (II) forms of copper, an increase in the intrinsic amount of copper quickly results in a considerable oxidative stress. Induction of oxidative stress leads to chromosomal aberration, micronuclei formation and DNA damage, indicative of genotoxicity. According to the Haber-Weiss and Fenton processes, under aerobic conditions, redox potential permits copper to create hydroxyl radicals [43]. Lipids, proteins, and nucleic acids are damaged when ROS are released, and finally all genetic material is destroyed [44, 45]. Researchers looked into the toxicity of CuO nanoparticles (NPs) to human lung epithelial (A549) cells [46-52]. While CuO bulk particles (BPs) shown significantly reduced toxicity (24-hour IC50s of 58 and 15 mg/L for CuO BPs and NPs, respectively), CuO NPs (10–100 mg/L) demonstrated considerable toxicity to A549 cells. CuO NPs were primarily absorbed by endocytosis. CuO NPs (15 mg/L) caused mitochondrial depolarization, which may have been caused by the production of reactive oxygen species (ROS). When intracellular CuO NPs are present, they first produce ROS, which then triggers the production of p38 and p53 and damages DNA [52]. Table 3 shows genotoxic potential of different organisms exposed to copper oxide nanoparticles of different sizes and shapes with their respective effects.

6. CONCLUSION

Copper is an essential nutrient that is required by almost all living organisms, including humans and its deficiency can lead to various health problems. It is required for the activity of various enzymes, including SOD, which protects cells against oxidative stress by scavenging superoxide radicals. Copper plays vital role in numerous physiological and biochemical processes, such as energy production, also involved in synthesis of hemoglobin, collagen and neurotransmitters production. It has shown significant medical potential, particularly in areas of antimicrobial activity and cancer therapy. In addition to this it also shows cardio protective effects and have potential role in wound healing, neurodegenerative disorders. Despite its essentiality for many biological processes, it can also be toxic at high concentrations leading to a range of health effects. Copper toxicity is characterized by the disruption of cellular processes, including oxidative stress, DNA damage and apoptosis. Copper can generate ROS, which are highly reactive molecules that can damage cellular components, including DNA, proteins, and lipids. It also affects the stability of chromosome and lead to micronuclei formation which are indicative of genotoxicity. It can be concluded that though copper is an essential nutrient but its excessive intake can lead to toxicity, therefore, it is important for individuals to consume an adequate but not excessive amount of copper through diet and to be aware of potential sources of copper exposure in occupational settings. Further research is needed to fully understand the therapeutic potential of copper and also to test the toxicity profiling of the newly synthesized copper based drugs and nanoparticles.

Table 3. Genotoxic potential of CuO NPs in different organisms.

Organism	Shape	Size	Effect	Ref.
Frog	Polydispersed	6 nm <100 nm <6 nm	NPs <100 nm more toxic than 6 nm, reduced cell viability, reduced GSH, cell death.	[45]
***Danio rerio* (Zebra fish)**	Polydispersed	<50 nm	Cross cell membrane, Release Cu^{2+}, ROS production, DNA damage, cell death, cell apoptosis	[46]
Mice	Nearly Spherical	<30- >80 nm	Cell apoptosis	[47]
Mouse	Spherical	30 – 40 nm	DNA methylation, DNA fragmentation, Chromosomal Damage, Lipid peroxidation, Micronucleus formation.	[48]
Rat	Spherical	15 – 20 nm	Inflammation, cell proliferation, upregulation of proinflammatory cytokine.	[49]
Human	Spherical	<100 nm	DNA lesions, DNA damage, neurotoxicity, cytotoxicity	[50]
Human	Spherical	50 nm	DNA damage through lipid peroxidation and oxidative stress, apoptosis	[51]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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