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Review Article

Biotechnology Section

Delineating the Mechanisms of Action of Copper-based Therapeutics: A Comprehensive Narrative Review

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ABSTRACT

Copper-based therapeutics have emerged as a promising frontier in modern metallopharmaceutical research. Copper possesses properties of unique redox activity, coordination flexibility, and multifaceted biological functions. This review discusses the metabolic significance of essential metals in human physiology, with particular emphasis on copper and its therapeutic potential. Copper plays indispensable roles in mitochondrial respiration, antioxidant defence, neurotransmitter synthesis, connective tissue formation, and iron metabolism through various copper-dependent enzymes and transport systems. The dualistic nature of copper, being both essential and potentially cytotoxic, forms the mechanistic basis for its biomedical applications. Copper complexes, nanoparticles, ionophores, and chelators exhibit remarkable anticancer and antimicrobial properties by inducing Reactive Oxygen Species (ROS) generation, DNA damage, proteasome inhibition, mitochondrial dysfunction, and the recently identified pathway of cuproptosis. Furthermore, advancements in nanotechnology and targeted delivery systems have improved the specificity, bioavailability, and therapeutic efficacy of copper-based agents while minimising systemic toxicity. Despite challenges related to stability and controlled delivery, copper therapeutics represent a highly versatile and cost-effective approach for combating cancer, multidrug-resistant infections, and redox-associated diseases. This review finds its necessity for a comprehensive understanding of copper metabolism, biological functions and its therapeutic applications. It highlights the growing significance of copper-based therapeutics in next-generation medicinal chemistry and translational biomedical research.

Keywords: Anticancer therapy, Antimicrobial activity, Copper nanoparticles, Cuproptosis, Reactive oxygen species, Targeted drug delivery

INTRODUCTION

Transition metals are integral to biological systems, serving as catalytic cofactors, structural components, and cellular regulators [1-3]. Their therapeutic potential has been exploited in metallodrugs, most notably platinum compounds like cisplatin in oncology [4,5]. Yet platinum-based therapies are hampered by toxicity, poor selectivity, and drug resistance [6,7]. These challenges have driven the exploration of alternative metals viz., gold, ruthenium, and copper. Among these, copper has emerged partially as candidate due to its dualistic biological nature; it is both essential for life and cytotoxic when dysregulated [8-11]. It supports mitochondrial respiration, angiogenesis, neurotransmitter synthesis, and antioxidant defence via enzymes including cytochrome C oxidase and Superoxide Dismutase (SOD) [12-16]. Its redox cycling between Cu(I) and Cu(II) drives ROS generation, promoting oxidative stress and cell death [17,18].

This contradiction forms the foundation of copper-based therapeutics. By exploiting the heightened sensitivity of cancer cells and pathogenic microorganisms to oxidative stress, copper can be selectively utilised to induce cytotoxicity in diseased cells while minimising damage to normal tissues. However, free copper ions are virtually absent in biological systems due to their toxicity [19-21]. Instead, copper exists in tightly regulated, protein-bound forms, coordinated by chaperones and transport systems that control its uptake, distribution, and storage. The concept of "bound copper pools" highlights the dynamic and compartmentalised nature of intracellular copper, emphasising the importance of understanding copper-protein interactions in both physiology and disease [22,23].

Copper coordination complexes formed with Schiff bases, phenanthroline derivatives, peptides, and heterocyclic ligands improve stability, solubility, and biological selectivity. Copper nanoparticles (CuNPs) further extend these capabilities by enhancing cellular uptake and targeted delivery, while copper ionophores elevate intracellular copper levels to induce cytotoxicity via oxidative stress and mitochondrial dysfunction [24].

Copper and its alloys, exhibit broad-spectrum antimicrobial activity [25,26]. The release of copper ions from these surfaces damages cell membranes, disrupts enzymatic systems and also generates ROS through Fenton-like reactions. Copper-based antimicrobial strategies have turned out substituting the threat of MDR [27,28]. These complexes have demonstrated promising efficacy against resistant pathogens. Copper cluster molecules (CuCs) are now being used for disrupting bacterial cell walls [29,30]. Copper containing drugs find the niche of applicability in cancer therapy too. It is due to the heightened copper demand of the cancer cells to sustain angiogenesis, proliferation, and metastasis [31-33]. These applications are most commonly carried out through copper chelation strategy or oxidative damage caused by excessive copper loading [33,34]. The Warburg effect further sensitises cancer cells to ROS-mediated injury. Copper coordination compounds target multiple cellular pathways to treat cancer [35,36]. DNA damage, telomerase inhibition, proteasome disruption, and apoptosis induction are some of the reported strategies.

The versatility of Copper's coordination chemistry influences the diverse biological functions of copper-dependent enzymes, such as cytochrome C oxidase, dopamine β-hydroxylase, tyrosinase, lysyl oxidase, and Cu/Zn- SOD [37-39]. Although it can exist in multiple oxidation states (+1, +2, and +3), the +2 state is the most stable in biological systems. Typically, it forms complexes with coordination numbers ranging from four to six. In humans, the body contains approximately 100 mg of copper, absorbed via the gastrointestinal

tract, transported through blood proteins to the liver, and excreted primarily via bile. Recent advancements have also explored the use of radioactive copper isotopes in theranostics, where a single molecule can be used for both diagnosis and therapy by altering the isotope. This dual functionality highlights the expanding role of copper in modern medicine.

Despite the promising potential of copper-based therapeutics, several challenges remain. These include limited selectivity, potential systemic toxicity, and an incomplete understanding of copper interactions at the molecular level under physiological conditions. The gap between successful laboratory findings and clinical translation underscores the need for further research into copper homeostasis, transport mechanisms, and targeted delivery systems.

Role of Different Metals in Human Metabolism

Metals are indispensable components of human biology and metabolism. They participate in virtually every physiological process, ranging from oxygen transport and cellular respiration to immune regulation and signal transduction [40,41]. Unlike organic nutrients that mainly serve as energy sources or structural molecules, metals function predominantly as catalytic and regulatory agents. Their unique physicochemical properties, particularly their ability to donate and accept electrons or coordinate with biomolecules, make them essential for sustaining life.

Metals in the human body are broadly categorised into macroelements and trace elements. Macroelements such as calcium, magnesium, sodium, potassium, and phosphorus are required in large quantities to maintain structural integrity and physiological stability [41,42]. Trace metals, including iron, copper, zinc, manganese, selenium, and molybdenum, are needed in much smaller concentrations but are equally vital because of their role in enzymatic reactions, antioxidant defence, and metabolic control.

Copper participates in mitochondrial energy production, antioxidant defence systems, neurotransmitter synthesis, connective tissue formation and iron homeostasis. Its remarkable ability to alternate between Cu(I) and Cu(II) oxidation states allows it to mediate electron transfer reactions efficiently. However, this same property also renders copper potentially toxic if not tightly regulated. Consequently, copper metabolism is governed by highly specialised transporters, chaperones, and storage proteins that maintain a delicate balance between physiological necessity and cellular toxicity.

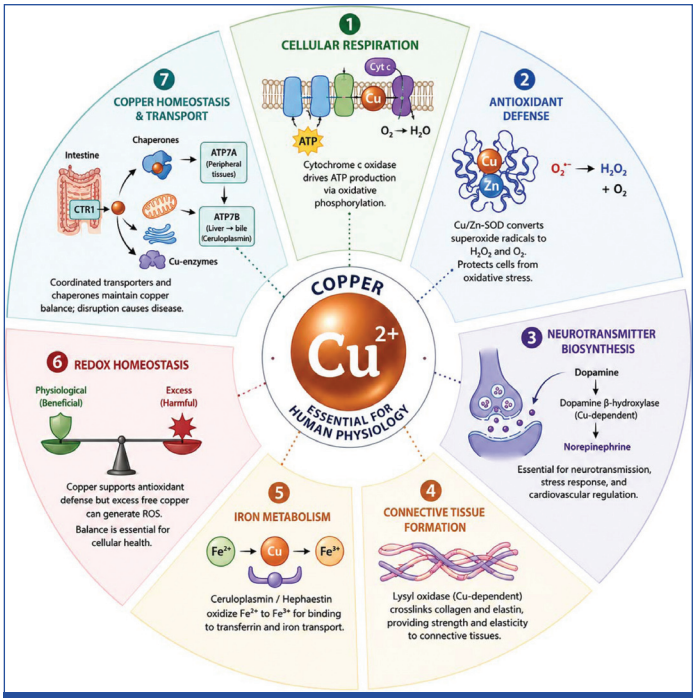
Copper: A Central Metal in Human Metabolism

Copper contributes to energy production, antioxidant defence, neurotransmitter biosynthesis, collagen maturation, immune regulation and iron metabolism. Additionally, copper metabolism is tightly regulated through coordinated systems of transport, storage, and excretion. Below stated are some of the essential metabolisms [Table/Fig-1].

a. **Copper in cellular respiration:** One of the most important copper-dependent enzymes is cytochrome C oxidase, the terminal enzyme of the mitochondrial electron transport chain. This enzyme catalyses the transfer of electrons from cytochrome C to molecular oxygen, reducing oxygen to water.

   Copper centres within cytochrome C oxidase facilitate electron transfer and proton translocation across the inner mitochondrial membrane. The resulting electrochemical gradient drives ATP synthesis through oxidative phosphorylation. Impaired copper availability can therefore compromise cellular energy production and mitochondrial function [43,44].

b. **Copper and antioxidant defence:** Copper is a catalytic component of Cu/Zn- SOD1, a critical antioxidant enzyme. During aerobic metabolism, superoxide radicals are continuously generated as byproducts of mitochondrial respiration. If not neutralised, these radicals can damage proteins, lipids, and nucleic acids. The SOD1 catalyses the conversion of superoxide radicals into hydrogen peroxide and molecular oxygen. Copper mediates the redox cycling necessary for this reaction, while zinc stabilises the enzyme structure. This defence mechanism protects cells from oxidative stress and preserves cellular integrity [45-47].



[Table/Fig-1]: Diagrammatic representation of different Cu2+ dependent human metabolism. (image credits- This is an AI-generated image showcasing the different roles of copper).

c. **Copper in neurotransmitter biosynthesis:** Copper-dependent enzymes are essential for nervous system function. One such enzyme, dopamine β-hydroxylase, catalyses the conversion of dopamine to norepinephrine, a key step in neurotransmission and the regulation of stress and cardiovascular responses [48,49]. Consequently, copper deficiency can disrupt neurotransmitter synthesis, leading to neurological and cognitive impairments.

d. **Copper in connective tissue formation:** Lysyl oxidase is a copper-dependent enzyme that catalyses the oxidative deamination of lysine residues. It facilitates collagen and elastin crosslinking within connective tissues [50,51]. These crosslinks are essential for maintaining the strength and elasticity of the skin, blood vessels, cartilage, and ligaments, while impaired copper metabolism disrupts this process and compromises tissue integrity.

e. **Copper and iron metabolism:** Copper is associated to systemic iron homeostasis. It occurs through copper-dependent multicopper ferroxidases, viz., ceruloplasmin and hephaestin. These enzymes oxidise Fe^{2+} exported by ferroportin to Fe^{3+}. Thus, it enables the loading onto transferrin. Transferin is the principal plasma iron-transport protein. Ceruloplasmin facilitates iron mobilisation from storage and recycling sites, including hepatocytes and macrophages, whereas hephaestin is particularly important for iron efflux from intestinal enterocytes. Consequently, copper deficiency can impair ferroxidase activity and lead to tissue iron accumulation together with reduced circulating iron and copper-deficiency-associated anaemia, even when total body iron stores are adequate or increased [52,53].

f. **Copper in redox homeostasis:** Copper occupies a dual role in oxidative biology. Under physiological conditions, copper supports antioxidant defence through copper-dependent

enzymes. However, excess free copper can catalyse Fenton-like reactions that generate hydroxyl radicals and other ROS [54]. Controlled ROS production is important for immune signalling, apoptosis, and cellular communication. Nevertheless, excessive ROS generation contributes to lipid peroxidation, DNA damage, protein oxidation, and chronic disease progression. Maintaining copper homeostasis is therefore essential for balancing beneficial and harmful redox reactions [55].

g. **Copper homeostasis and transport:** Copper homeostasis is maintained through a highly coordinated network of transporters, chaperones, and storage proteins. Dietary copper is absorbed in the intestine primarily through copper transporter 1 (CTR1). Once inside cells, copper is escorted by specialised chaperones to mitochondria, the Golgi apparatus, or copper-dependent enzymes. ATP7A and ATP7B are ATP-dependent transporters responsible for copper distribution and excretion. ATP7A delivers copper to peripheral tissues, whereas ATP7B mediates hepatic copper excretion into bile and incorporation into ceruloplasmin [54].

Disturbances in these transport systems result in severe metabolic disorders. Wilson's disease, caused by mutations in ATP7B, leads to toxic copper accumulation in the liver and brain. Menkes disease, resulting from ATP7A mutations, causes systemic copper deficiency and impaired activity of copper-dependent enzymes [56-58].

Metal-based therapeutics: Metal-based therapeutics plays a pivotal role in modern medicinal chemistry because of their unique pharmacological properties. These include diverse oxidation states, coordination geometries and redox activities. Platinum-based drugs such as cisplatin, carboplatin and oxaliplatin are seen to be commonly used in cancer therapy. These agents primarily exert their anticancer effects by binding covalently to DNA. The covalent bonds form intra- and inter-strand crosslinks in DNA disrupting the replication and transcription. Despite their remarkable clinical efficacy, platinum drugs are associated with significant limitations, such as nephrotoxicity, neurotoxicity, cytotoxicity and poor tumour selectivity.

Gold-based therapeutics, on the other hand, do not target DNA directly but instead interfere with cellular redox regulation by inhibiting thioredoxin reductase. Thus, it disrupts redox homeostasis in cancer cells. This distinct mechanism makes gold compounds particularly promising for treating redox-dependent malignancies and has also highlighted their potential as antimicrobial agents. Ruthenium complexes represent another important class of metallodrugs because they exhibit lower systemic toxicity and can undergo selective activation under the hypoxic conditions commonly found in solid tumours. Thus, these diverse mechanisms highlight the expanding role of metal-based therapeutics in the development of more selective and effective treatments for cancer and other diseases.

In contrast to other metals, copper complexes often act through broader cellular stress pathways rather than relying on a single dominant target, which may reduce the chance of resistance [59]. Copper is considered for cancers and other diseases where redox imbalance, mitochondrial vulnerability, or altered metal homeostasis can be exploited therapeutically [60].

Although, the current article advocates the Copper, it also important to note that mere being endogenous, one cannot claim an absolute safety. Free or poorly controlled copper can damage healthy tissues through oxidative injury, so successful copper therapeutics depend on precise molecular design, controlled release, and selective accumulation in diseased cells [10,11]. The current direction of the field is therefore not just to use copper, but to use it intelligently, in ways that harness its biological relevance without unleashing nonspecific toxicity.

Mechanistic Basis of Copper-Based Therapeutics

Copper-based therapeutics are distinguished by their multi-target. The synergistic mechanisms of actions enable them to disrupt multiple cellular pathways simultaneously. This poly-pharmacological behaviour of copper therapeutics, is a major advantage over conventional single-target drugs. This helps in reducing the likelihood of resistance and enhances therapeutic efficacy. The essential mechanisms include ROS generation, DNA damage, proteasome inhibition, and enzyme modulation, each contributing to cellular dysfunction and ultimately cell death.

Reactive Oxygen Species (ROS) generation: A central hallmark of copper-based therapeutics is their ability to catalyse redox cycling between Cu(I) and Cu(II). This leads to the generation of ROS [61,62]. The generated ROS are hydroxyl radicals (•OH), superoxide anions (O_2•–), and hydrogen peroxide (H_2O_2). At the molecular level, ROS-mediated damage leads to lipid peroxidation, protein oxidation, enzyme inactivation, and DNA strand breaks [60,61,63]. Cancer cells due to metabolic reprogramming (e.g., the Warburg effect), are particularly vulnerable to further ROS accumulation, resulting in selective cytotoxicity. Additional ROS accumulation overwhelms antioxidant defences and selectively induces cytotoxicity in malignant cells, sparing normal cells with stronger antioxidant systems [64,65]. This selective vulnerability is one of the major therapeutic advantages of copper-based agents.

DNA damage and genomic instability: Copper complexes can directly or indirectly interact with DNA, causing structural and functional disruption of the genome. Reports of single and double strand breaks are found caused due to binding of copper complexes within the minor groove of DNAs [66]. These interactions promote oxidative lesions such as 8-oxoguanine and impair DNA replication and transcription, ultimately activating DNA damage response pathways and apoptosis [67]. Copper complexes can also inhibit DNA repair enzymes. These amplifies genomic instability and cytotoxicity [35,36]. The integrated effect is a sustained disruption of cellular homeostasis that contributes significantly to anticancer efficacy.

Proteasome inhibition: Copper-based therapeutics can inhibit the Ubiquitin–Proteasome System (UPS) [68]. It is a pathway essential for maintaining protein homeostasis. Copper complexes interfere with the catalytic core of the proteasome, thus accumulating ubiquitinated and misfolded proteins [69]. This accumulation triggers endoplasmic reticulum stress and activates unfolded protein response pathways that culminate in apoptosis [70,71]. Since cancer cells exhibit elevated protein turnover and metabolic demand, they are especially dependent on efficient proteasomal function. Consequently, proteasome inhibition selectively induces cytotoxicity in malignant cells [72,73]. This mechanism complements ROS-mediated oxidative damage and reinforces the multi-target behaviour of copper therapeutics.

Mitochondrial dysfunction and apoptosis induction: Mitochondria are major intracellular targets of copper-mediated toxicity. Copper accumulation within mitochondria disrupts electron transport chain activity [74]. This impairs oxidative phosphorylation, and hence decreases the ATP production. This disruption increases electron leakage and enhances ROS generation within the mitochondrial matrix. The resulting mitochondrial dysfunction leads to loss of mitochondrial membrane potential ($\Delta\Psi m$), release of cytochrome C, and activation of intrinsic apoptotic pathways through caspase signalling [75,76]. Copper-induced mitochondrial damage also compromises metabolic flexibility, particularly in cancer cells that rely on altered metabolic pathways for survival [77-80]. This mitochondrial targeting is particularly effective in cancer cells, which depend heavily on metabolic flexibility.

Cuproptosis: A novel copper-dependent cell death pathway: Cuproptosis represents a unique regulated cell death pathway

distinct from apoptosis, necrosis, and ferroptosis [81,82]. Mechanistically, cuproptosis occurs through direct binding of copper to lipoylated proteins within the Tricarboxylic Acid (TCA) cycle. Protein lipoylation is a post-translational modification where lipoic acid is covalently attached to specific lysine residues. Cuproptosis leads to protein aggregation and destabilisation of iron-sulfur cluster proteins [83,84]. These events induce severe proteotoxic stress and metabolic collapse, ultimately resulting in cell death [85]. Tumours cells heavily dependent on mitochondrial respiration are particularly susceptible for cuproptosis [86].

Copper coordination complexes and chelators: Copper coordination complexes constitute one of the most extensively investigated classes of copper therapeutics. These complexes are formed through interactions between copper ions and ligands such as Schiff bases, phenanthroline derivatives, peptides, and heterocyclic molecules [36,87,88] Ligand coordination stabilises copper in biologically compatible forms and enables selective interaction with cellular targets [89]. Copper chelators, in contrast, modulate copper availability within biological systems [55]. Compounds such as disulfiram can form copper complexes that inhibit proteasome activity and induce apoptosis in cancer cells [90,91]. These approaches demonstrate that copper modulation can either deprive pathological cells of copper or exploit copper overload to induce cytotoxicity.

Nanotechnology and targeted copper delivery: Nanotechnology-based delivery systems have transformed copper therapeutics by improving bioavailability, pharmacokinetics, and controlled release [92,93]. Liposomes, polymeric nanoparticles, and Metal–Organic Frameworks (MOFs) provide controlled delivery and targeted accumulation of copper within diseased tissues. Passive targeting strategies exploit the enhanced permeability and retention effect in tumours, whereas active targeting incorporates ligands that recognise overexpressed receptors on cancer cells [94,95]. Stimuli-responsive systems further improve specificity by releasing copper under acidic pH, altered redox conditions, or disease-specific enzymatic activity [96,97]. These advanced delivery systems reduce systemic toxicity, improve therapeutic precision, and support theranostic applications that combine therapy with imaging [98,99].

Antibacterial and Antimicrobial Activity

Copper exhibits potent broad-spectrum antimicrobial activity through membrane disruption, protein denaturation, DNA damage and ROS generation [100,101]. Copper ions destabilise microbial membranes, impair enzymatic systems, and induce genomic instability [102,103]. A major advantage of copper is its efficacy against MDR pathogens such as *Staphylococcus aureus* and *Escherichia coli* [104-106]. It is due to copper's property of simultaneously targeting multiple cellular pathways that microorganisms lose the ability in developing resistance [46]. This multi-target antimicrobial mechanism positions copper as a promising alternative to conventional antibiotics in combating antimicrobial resistance.

Advantages, Limitations, and Clinical Perspective

Copper-based therapeutics offer significant advantages, including multi-target activity, reduced drug resistance, cost-effectiveness, and combined anticancer and antimicrobial potential. They exert their effects by inducing oxidative stress, mitochondrial dysfunction, DNA damage, and disruption of cellular signalling pathways. However, challenges such as systemic toxicity, limited stability, poor bioavailability, rapid clearance, and unresolved pharmacokinetic and safety concerns continue to hinder their clinical translation. Recent advances in nanotechnology, ligand engineering, ionophore development, AI-assisted drug discovery, and the identification of cuproptosis are accelerating the development of safer and more effective copper-based therapeutics.

Future Perspectives

The future of copper-based therapeutics depends on overcoming current limitations while exploiting emerging technologies. Combination therapies with chemotherapy, antibiotics or targeted agents can enhance efficacy. It can overcome drug resistance and reduce toxicity by leveraging copper's multi-target mechanisms, including ROS generation, proteasome inhibition and mitochondrial disruption. Advances in targeted delivery systems, particularly passive, active, and stimuli-responsive strategies, are expected to improve treatment specificity and minimise off-target effects. Nanotechnology-based carriers, such as liposomes, polymeric nanoparticles, and MOF, offer controlled drug delivery, targeted release and theranostic capabilities for real-time treatment monitoring. Further investigation of copper-protein interactions, cuproptosis, and copper-dependent signalling pathways will deepen understanding of disease mechanisms and identify novel therapeutic targets. In addition, integrating artificial intelligence and bioinformatics with experimental research will accelerate drug discovery, optimise ligand-metal interactions, and streamline the development of safer and more effective copper-based therapeutics.

CONCLUSION(S)

Copper has gained considerable attention as a biologically important transition metal with broad therapeutic potential due to its unique physicochemical and biochemical properties. Its redox activity, diverse coordination chemistry, and indispensable role in cellular metabolism allow copper-based compounds to modulate multiple biological pathways simultaneously. These compounds exert their therapeutic effects through mechanisms such as ROS generation, DNA damage, proteasome inhibition, mitochondrial dysfunction, and the recently recognised process of cuproptosis. Unlike many conventional metallodrugs that target a single molecular pathway, copper complexes demonstrate multi-target activity, making them particularly effective against multifactorial diseases, including cancer and MDR microbial infections. Furthermore, the natural abundance and relatively low cost of copper enhance its suitability for large-scale therapeutic development. Nevertheless, challenges such as systemic toxicity, limited stability, and inefficient targeted delivery continue to hinder their widespread clinical application. Encouragingly, recent advances in nanotechnology, targeted drug delivery strategies, and a deeper understanding of copper homeostasis have significantly improved the safety and efficacy of copper-based therapeutics. Overall, copper represents a promising platform for the development of next-generation metal-based medicines. Future progress will depend on interdisciplinary efforts combining medicinal chemistry, molecular biology, nanotechnology, pharmacology, and computational approaches to optimise therapeutic performance and accelerate the translation of copper-based compounds from laboratory research to clinical practice.

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