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The Potential Therapeutic Applications of Copper and Its Complexes and Copper Chelation Therapy

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Abstract

Copper, a vital trace element, is integral to various biological functions, including cellular respiration, free radical detoxification, iron metabolism, neurotransmitter production, and angiogenesis. This transition metal exhibits distinctive redox characteristics that render it a versatile therapeutic agent across various disease domains. This review study examines the potential functions of copper and its complexes in anti-cancer, anti-microbial, and anti-inflammatory therapy, as well as the application of copper nanoparticles in wound healing processes. The concentration of copper must be meticulously monitored, as any deviation in its homeostasis can lead to abnormalities. One of the most promising strategies for sustaining physiological copper levels is copper chelation therapy, which has emerged as a vital treatment for neurodegenerative disorders, including Wilson's disease, Alzheimer's disease, as well as conditions such as diabetes mellitus and idiopathic pulmonary fibrosis. Besides demonstrating significant biocidal qualities, copper is also linked to skin health.

The comprehensive understanding of the bioinorganic characteristics of copper and its complexes, alongside the novel prospects presented by advancements in medicinal chemistry, is facilitating the identification of a new category of highly efficacious pharmaceuticals with minimal side effects, potentially enhancing clinical research and practice significantly.

Keywords: *Copper, copper complexes, anti-cancer agent, anti-microbial agent, copper nanoparticles, neurodegenerative disorders, anti-arthritic drugs, copper chelation therapy.*

1. Introduction

Copper, similar to essential amino acids and essential fatty acids, is a vital microelement required for normal metabolic processes (Brewer,2009). Nonetheless, it cannot be produced via de novo pathways, making dietary consumption essential. Copper demonstrates considerable metabolic activity, serving as either a vital trace element or a key component of various substances introduced externally to individuals. Initially, it attaches to proteins such as albumin and ceruloplasmin; thereafter, it interacts with different ligands to create complexes that connect with biomolecules, primarily proteins and nucleic acids (Delimaris et al.,2008). Copper-binding proteins, including cytochrome oxidase, copper-zinc-superoxide dismutase, lysyl oxidase, tyrosinase, and dopamine-beta-monooxygenase, play a crucial role

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in vital biological processes such as mitochondrial respiration, antioxidant defense, extracellular matrix cross-linking, pigmentation, and neurotransmitter biosynthesis (Kim et al.,2008). Copper is primarily found in organs that exhibit high metabolic activity, such as the liver, kidneys, heart, and brain. About five percent of the total copper in the body is found in serum, with nearly 95% of this quantity associated with ceruloplasmin. The standard range of copper levels in healthy individuals is roughly 50–120 mg. The regulation of copper concentration is essential, as unbound copper acts as a strong oxidant, resulting in the formation of highly reactive hydroxyl radicals that can harm proteins, lipids, and DNA (Uriu-Adams & Keen,2015). Homeostatic processes, such as absorption, elimination, and bioavailability, meticulously regulate the concentration of copper in cells (Kaplan & Maryon,2016). The primary protein responsible for copper import is Copper transporter 1, which is situated on the cell membrane. ATPase copper-transporting alpha (ATP7A) and ATPase copper-transporting beta (ATP7B) are essential for maintaining copper balance, enabling the movement of copper to the secretory pathway and the removal of excess copper from the cell (Bandmann et al.,2015). Copper readily transitions between its two oxidation states, Cu(I) and Cu(II). Copper ions in the body demonstrate notable redox activity and promote electron transfer in both the +1 and +2 oxidation states, essential for enzyme-catalyzed processes, including biological redox reactions. Copper serves dual roles as both a valuable and harmful component within a cell. A developing collection of in vitro and in vivo studies indicates that copper-based mechanisms could act as promising therapeutic targets for a range of diseases. The current investigation primarily focuses on the regulation of copper levels within biological systems. The connection between copper and tumors reveals that individuals with cancer show increased copper concentrations in their serum and tissues, implying that the presence of malignancy might interfere with the body's regulation of copper levels. Studies indicate that copper facilitates angiogenesis, metastasis, and the development of tumors (Harvey et al.,2013; Tapiero et al.,2003). Multiple investigations suggest that increased levels of copper can have detrimental impacts on cancer cells. Oral copper chelators have demonstrated the ability to inhibit tumor growth and metastasis in both human patients and animal cancer models (Lopez at al.,2019). Copper-based compounds demonstrate promising anti-cancer properties. Copper is acknowledged as a vital component of the innate immune system, functioning as a key line of defense against invading pathogens. Small-molecule ligands offer a promising avenue for therapeutic mimicry of the immune system; however, the use of free copper is not appropriate due to its absence of host-pathogen selectivity. Moreover, numerous studies have highlighted the antiviral and antibacterial characteristics of Cu (II) complexes (Borkow & Gabbay,2014). Extended contact with copper surfaces has demonstrated a decrease in the infectivity of the influenza A virus (Noyce et al.,2007). Numerous well-known therapeutic agents, including pyrithione and disulfiram, exhibit notable inhibitory effects that are dependent on copper. The implementation of high-throughput screens resulted in the identification of multiple novel compounds that function as copper-dependent inhibitors targeting Staphylococcus aureus and Mycobacterium tuberculosis (Jimenez-Garrido,2005). Copper complexes show promise as anti-inflammatory agents and could be important in anti-arthritic therapies, as indicated by multiple reviews. Cupric carbonate and cupric complexes show effectiveness in reducing inflammation. A variety of Cu (II) complexes formed with non-steroidal anti-inflammatory drugs (NSAIDs) exhibit improved anti-inflammatory and antiulcerogenic effects, as well as decreased gastrointestinal toxicity, when compared to traditional uncomplexed medications (Crisponi et al.,2010). Copper chelation therapy serves as a viable treatment approach for conditions in which an imbalance of copper plays a crucial role in disease development. This encompasses idiopathic pulmonary fibrosis, diabetes, neurodegenerative conditions such as Parkinson's and Alzheimer's, as well as genetic disorders related to copper metabolism, including Wilson's disease. Copper chelating agents, such as trientine are considered safe for application in individuals with Wilson's disease and those undergoing cancer treatment (Weiss et al.,2013). Copper serves as a bioactive nanoparticle, demonstrating intricate functions across diverse cellular environments. This plays a crucial role in the mechanisms of action of growth factors and cytokines, being fundamentally involved in every stage of the wound healing process. Copper plays a crucial role in angiogenesis, skin regeneration, and enhancing the healing process (D et al.,2021). Although there is a wealth of information on the effects of copper on individuals, the function of copper complexes in the medical field is still not fully comprehended, and the clinical significance of copper status is not consistently well-defined. These substances seem to hold significant importance in medical processes, and their value may have

been overlooked. This study seeks to examine the current body of literature regarding the physiological roles of copper, with an emphasis on the biochemical effects of copper complexes and their possible therapeutic uses.

2. METABOLISM AND REGULATION OF COPPER

The Copper Transporter 1 protein (CTR1) functions as the main pathway for the uptake of copper into cells (Galler et al.,2020). Copper is transported to CCS, COX17, and ATOX1 after it enters the cell. SOD1 (superoxide dismutase 1) obtains copper from CCS, playing a crucial role in safeguarding against oxygen toxicity. Cytochrome c oxidase (CCO), crucial for mitochondrial respiration, obtains copper from COX17 (Kim et al.,2008). The transport of copper into the cell nucleus occurs via ATOX1, which subsequently promotes the expression of G1/S-specific cyclin D1, thereby aiding in the process of cell division (Itoh et al.,2008).

The Golgi network's complex transport mechanisms enable ATOX1 to regulate the subcellular distribution of copper, facilitating its transfer to ATP7A and ATP7B throughout the network (Gudekar et al.,2020). To prevent copper toxicity, MT and GSH sequester surplus copper within the cell. Additionally, ATP7A (ATPase copper transporting alpha) and ATP7B (ATPase copper transporting beta) primarily serve to enable the efflux of copper ions from cells. Copper plays an essential role as a transition metal, participating in numerous critical processes; however, it can exhibit toxic effects in biological systems if not properly regulated. While Cu (II) represents the predominant redox state in the bloodstream, Cu(I) is the reduced form that is more commonly observed within cells. Cu (II) undergoes reduction to Cu(I) through various mechanisms prior to absorption by the cells. To avert cellular damage caused by copper, biological systems employ specialized proteins that meticulously regulate the absorption, transport, and excretion of copper, as well as its allocation to specific copper-binding protein sites where this metal is essential (Macomber & Imlay,2009).

3. COPPER AS ANTI-CANCER AGENT

Patients with acute leukaemia exhibit elevated levels of copper in their serum or plasma (Tisato et al.,2010). An increase in bone marrow blast cells was associated with a rise in serum copper levels (Deng et al.,2006). The relationship between lowered serum copper levels and the alleviation of symptoms or remission after treatment has streamlined the process of making predictions based on blood copper assessments. The following image demonstrates the relationship between copper and cancer.

A key characteristic of cancer cells is their ability to evade cell death, which plays a significant role in their resistance to treatment. Inducing cell death through the targeting of copper ions can facilitate the differentiation of cancer cells from healthy cells, given the increased copper enrichment observed in cancerous tissues. Currently, a highly discussed area in the advancement of anti-cancer therapies is the focus on copper targeting. Currently, there are two main strategies for addressing cancer that focus on copper targeting. Initially, we have copper chelators such as trientine, TTM, and D-penicillamine (Nagai et al.,2012; Tawari et al.2015). These medications function to combat cancer by interacting with copper and reducing its bioavailability. Copper ionophores encompass compounds such as disulfiram and elesclomol (Tsvetkov et al.,2022). The generation of reactive oxygen species, inhibition of the proteasome, and induction of apoptosis enable these carriers to elevate intracellular copper ion levels, thereby exhibiting anti-tumour effects (Liu et al.,2015).

4. COPPER AS ANTI-MICROBIAL AGENT

Copper possesses inherent anti-microbial characteristics that effectively combat bacteria including Escherichia coli and Staphylococcus aureus, as well as viruses such as SARS-CoV2, Influenza A virus, and norovirus, along with fungi like Aspergillus and Candida species. Copper nanoparticles exhibit anti-microbial properties (Kaweeteerawat

et al.,2017). The activity of copper nanoparticles is influenced more by their size than by their concentration; smaller nanoparticles demonstrate greater effectiveness against microbes. The generation of reactive oxygen species, which harm membranes, serves as the main mechanism behind bactericidal action (Pham et al.,2013; Yang et al.,2014). The primary mechanism through which the copper surface exerted its antiviral effects was ion release, leading to RNA degradation and membrane breakage in enclosed viruses (Warnes et al.,2015). The primary processes involved in copper infiltration in fungi are believed to include the absorption of copper ions and the physical breakdown of the membrane (Muñoz-Escobar et al.,2020).

5. ROLE OF COPPER IN ANTI-INFLAMMATORY THERAPIES

Copper complexes constitute a unique class of anti-arthritic agents for two main reasons. Studies involving animals have shown that these agents are effective anti-ulcer treatments when evaluated against currently utilized ulcerogenic medications. Secondly, when compared to long-term treatment with current medications, short-term Cu complex therapy led to lasting remissions in the treatment of human rheumatic diseases (Soylak & Kirnap,2010). The dual aspects of copper complexes' biological activity, coupled with their proven anti-inflammatory properties in various animal models, indicate that therapy involving copper complexes could provide benefits compared to existing medication strategies. Cupric carbonate and cupric complexes of acetic, lauric, oleic, caprylic, butyric, sebacic, lipoic, and cinnamic acids showed effectiveness in animal models of inflammation (Patel et al.,2010).

6. COPPER CHELATION THERAPY

A chelator is a chemical entity that selectively interacts with particular atoms or ions, resulting in the formation of a stable, cyclic complex structure. Metal chelating compounds act as growth enhancers in aquaculture and are utilized as additives in various products such as cleaning agents, cosmetics, plastics, fertilizers, and nutritional supplements. Chelation therapy is utilized to eliminate toxic metals from the body as well as from soil environments. Clinically significant copper deficiency and copper overload toxicity are uncommon and mainly linked to genetic disorders in copper transport (Ding et al.,2011). Furthermore, there is a link between diabetes and neurological conditions with copper dyshomeostasis, resulting in its incorrect distribution. Different copper chelating agents, including D-penicillamine (S)-2-amino-3-mercapto-3-methylbutanoic acid, tetrathiomolybdate, and trientine, influence cellular copper levels via unique mechanisms (Lu,2010). The primary therapeutic approach of copper chelation therapy emerged after thorough investigation into the copper imbalance associated with Wilson's disease. This has greatly decreased morbidity and made Wilson's disease manageable (Mohr,2019). The focus is on assessing novel chelating agents and formulations to improve blood-brain barrier permeability, minimize adverse effects, and enhance patient compliance (Maher et al.,2015). Neurological disorders, including Alzheimer’s disease, are characterized by the extracellular accumulation of β-amyloid protein and its buildup in the brain (Sensi et al.,2018). Studies suggest that metal chelating agents may decrease excess β-amyloid protein, indicating that copper chelating agents like D-penicillamine could play a potential therapeutic role in individuals with Alzheimer’s disease (Squitti et al.,2002). Studies on idiopathic pulmonary fibrosis show that administering tetrathiomolybdate leads to lower serum ceruloplasmin levels, which is associated with a decrease in lung fibrosis (Ovet et al.,2014). Individuals diagnosed with diabetes mellitus demonstrate higher copper concentrations when contrasted with those who are healthy. The utilization of copper chelators to sustain copper homeostasis could represent a potential therapeutic approach for diabetes management. Metformin, acknowledged as a primary treatment for type II diabetes, diminishes the likelihood of vascular complications linked to the condition and shows promise as a therapeutic agent with chelating capabilities. Metformin demonstrates a greater affinity for copper and interacts with several transitional metals (Repiš˘cák et al.,2014; Foretz et al.,2019). In a mouse model of type II diabetes, TM treatment leads to a notable decrease in insulin

resistance (Tanaka et al.,2009).

7. APPLICATION OF COPPER TO IMPROVE THE WELL-BEING OF SKIN

Copper is essential for skin regeneration and angiogenesis, primarily through the induction of vascular endothelial growth factor (VEGF) and the action of hypoxia-induced factor-1-alpha (HIF-1α) (Zhou et al.,2020; Wu et al.,2019). This occurs through the elevation of HIF-1α expression and its subsequent binding to essential motifs within the promoter and potential enhancer regions of genes regulated by HIF-1. The antibacterial properties and low toxicity profile of copper nanoparticles make them excellent candidates for incorporation into wound dressings. Copper is crucial in the healing process under controlled conditions, as it enhances the expression of extracellular matrix components such as fibrinogen, collagen synthesis, and integrins, which serve as the main facilitators of cell attachment to the extracellular matrix (Sen et al.,2002).

8. CONCLUSION

Copper and its complexes have a wide range of potential applications in medicine, including wound healing, microbiology, cancer treatment, and anti-inflammatory therapies. Copper exhibits remarkable versatility due to its distinctive redox properties and capacity to engage with biomolecules; however, careful regulation of its concentration is essential to prevent toxicity. Studies show that copper acts as an effective therapeutic agent for various disorders and plays a vital role in maintaining physiological systems. Copper chelation therapy presents intriguing strategies for addressing conditions like idiopathic pulmonary fibrosis, diabetes, and neurological disorders.

Copper nanoparticles exhibit significant promise as antibacterial agents and in facilitating skin regeneration, thus expanding their therapeutic uses. Although progress has been made, additional investigation is necessary to comprehensively grasp the therapeutic potential of copper, given the complexities surrounding its clinical application in medicine. Progress in bioinorganic chemistry and clinical studies is anticipated to drive the creation of novel copper-based therapies, potentially leading to fewer side effects and enhanced effectiveness.

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