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Potential of Copper and its Complexes as Therapeutic Agents

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***Abstract*— The fundamental role of copper and the recognition of its complexes as important bioactive compounds in vitro and in vivo aroused an ever-increasing interest in these agents as potential drugs for therapeutic intervention in various diseases.The vast array of information available for their bioinorganic properties and mode of action in several biological systems, combined with the new opportunities offered by the flourishing technologies of medicinal chemistry, is creating an exciting scenario for the development of a novel generation of highly active drugs with minimized side effects which could add significantly to the current clinical research and practice. In this paper we attempt to summarize information on this trace metal and its complexes with respect to their importance in treating various diseases.**

***Index Terms*— Copper Complexes, Drug, Bioinorganics, Diseases.**

I. INTRODUCTION

Copper is recognized as an essential metalloelement like sodium, potassium, magnesium, calcium, iron, zinc, chromium, vanadium and manganese [1]**.** Like essential amino acids, essential fatty acids and essential cofactors (vitamins), essential metalloelements are required for normal metabolic processes but cannot be synthesized ***de*** *novo* and daily dietary intake and absorption are required. Copper exhibits considerable biochemical action either as an essential trace metal or as a constituent of various exogenously administered compounds in humans. In its former role it is bound to ceruloplasmin, albumin, and other proteins, while in its latter it is bound to ligands of various types forming complexes that interact with biomolecules, mainly proteins and nucleic acids. The multifaceted role of copper in biological systems is demonstrated by several studies. In particular the involvement of copper in human diseases has been described from a medicinal-chemical [2,3]and a biochemical viewfocusing on the molecular physiology of Cu transport[4]. Much of the current research effort is cited on copper homeostasis and its relation to iron metabolism as well as the role of copper in biological processes related to human physiology and pathology[5] while a lot of the functions that have been proposed to account for the homeostasis of inorganic non complexed copper in humans have been described[6] only a limited number of review studies have focused on the several biochemical events which could be directly implicated in the use of copper complexes in medicine. Current interest in Cu complexes is stemming from their potential use as antimicrobial, antiviral, anti-inflammatory, anticancer agents, enzyme inhibitors, or chemical nucleases. Markedly, the biochemical action of Cu complexes with non-steroidal anti-inflammatory drugs (NSAIDs) has been studied [7,8,9]. Numerous Cu(II) complexes of NSAIDs showing enhanced anti-inflammatory and antiulcerogenic activity, as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized[10]. They comprise a class of potential anti-inflammatory drugs with reduced side effects, and their mode of action is attributed to their marked superoxidedismutase- (SOD-) mimetic activity [11,12]. Copper is an essential transition metal that is required in vital biological processes in organisms under biological conditions, copper readily changes between two oxidation states namely, Cu(I) and Cu(II)[9]. This redox cycling property allows copper to act as a catalytic cofactor in enzymes, such as cytochrome c oxidase and Cu/Zn superoxide dismutase, for important biological processes. As such, copper contributes to mitochondrial ATP production and detoxification of reactive oxygen species (ROS), respectively [13,14].

Copper is also incorporated as a structural component in proteins [15,16] although copper is important for normal functioning of organisms, it can cause deleterious effects when its homeostasis is dysregulated. For instance, elevated serum and tissue copper levels were observed in cancer patients, suggesting that systemic copper homeostasis is altered by malignancy [15,17]. Indeed, copper has been shown to promote tumour growth and stimulate angiogenesis and metastasis [18]. Other studies have concentrated on the potential chemotherapeutic properties of copper-based compounds[19,20,21]. Moreover, several authors have brought to attention the antiviral and antibacterial activity of Cu(II) complexes. For instance, it was shown that the infectivity of influenza A virus is reduced after exposure on copper surfaces. The mechanism of this process is only partly understood, but it has been speculated the degradation of the viral nucleic acid takes place after the intervention of copper ions. In addition, the study and development of Cu complexes could be helpful in the design and production of antiviral and antibacterial materials, able to deactivate HIV or H1N1 viruses [22] and antibiotic resistant bacteria, respectively. Towards this direction, a method of producing copper-impregnated materials that possess broad-spectrum antimicrobial properties has been reported[18,19]. Despite the fact that the action of copper in humans has been intensively studied, the clinical picture of copper status is not always so straightforward, and less is known about the role of copper complexes in medicine. Yet it is evident that such compounds could be very important in medicinal procedures,

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and their role has probably been underestimated. The purpose of the present work is to review multiple physiological activities of copper and its complexes with particular focusing on their biochemical action and applications in ameliorating various disease conditions.

II. METABOLISM AND REGULATION OF COPPER

As a crucial transition metal, copper is involved in many vital processes, but can also have toxic effects in biological systems if not properly regulated. While Cu(II) is the predominant redox state in the blood, Cu(I) is the reduced form more commonly found intracellularly[23]. In fact, prior to the uptake of copper by cells, Cu(II) is reduced to Cu(I) by a variety of mechanisms, including plasma membrane reductases, including metalloreductases, such as duodenal cytochrome b561 (DCYTB/CYBRD1) and specific isoforms of the six-transmembrane epithelial antigen of the prostate (STEAP) family[19,24]. In the cell, Cu(I) has the potential to generate hydroxyl radicals (OH) from hydrogen peroxide via Fenton type and Haber-Weiss- type reactions.[25]. Hydroxyl radicals are able to react with a wide variety of biological molecules including proteins, lipids and DNA, leading to protein oxidation, lipid peroxidation and DNA strand breaks, respectively[17,25]If in excess, this results in extensive cellular damage leading either to carcinogenesis or cell death. Therefore, in order to prevent copper- mediated cellular damage, biological systems utilize specialized proteins to tightly regulate absorption, transportation and excretion of copper, and its delivery to copper binding protein sites that require this metal [1].

III. COPPER IN HUMAN HEALTH AND DISEASE

Copper in food (organic copper) is processed by the liver and is transported and sequestered in a safe manner. Inorganic copper, such as that in drinking water and copper supplements, largely bypasses the liver and enters the free copper pool of the blood directly [26]. This copper is potentially toxic because it may penetrate the blood/brain barrier [1]. About 50% of the average daily dietary copper of around 25 μmol (1.5mg) is absorbed from the stomach and the small intestine. Absorbed copper is transported to the liver in portal blood bound to albumin and is transmitted to peripheral tissues mainly bound to ceruloplasmin and, to a lesser extent, albumin. The liver contains 10% of the total body content of 1200 μmol (80 mg)[27]. Excess copper is excreted in bile into the gut, and the faecal copper output (12.5 μmol/24 h) is the sum of unabsorbed dietary copper and that re-excreted into the gut [28]. Copper homeostasis is regulated by alterations in both the absorptive efficiency and biliary excretion in the gut. At low and high intakes, the efficiency of absorption is regulated up and down, respectively, but is predominantly controlled via endogenous excretion [29]. Copper is incorporated into a number of metalloenzymes involved in hemoglobin formation, drug/xenobiotic metabolism, carbohydrate metabolism, catecholamine biosynthesis and the cross-linking of collagen, elastin, and hair keratin as well as in the antioxidant defense mechanism[30,31]. Moreover, copper-dependent enzymes, such as cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase, function to reduce reactive oxygen species (ROS) or molecular oxygen[3]. Symptoms associated with copper deficiency in humans include normocytic, hypochromic anemia, leukopenia, and osteoporosis. Copper deficiency is rarely observed in the general population [32].

Although copper homeostatic mechanisms play an important role in the prevention of copper toxicity, exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anemia, immunotoxicity, and developmental toxicity.[5] Many of these effects are consistent with oxidative damage to membranes or macromolecules. Given the capacity of copper to produce large amounts of reactive oxygen species (ROS), an excess of Copper could result in oxidative-stress-related health disorders, many of which can be linked partially to its redox reactivity. Copper has been suggested to facilitate oxidative tissue injury through a free-radical-mediated pathway analogous to the Fenton reaction [39]. By applying the electron spin resonance (ESR) spin-trapping technique, evidence for copper-mediated hydroxyl radical formation *in vivo* has been obtained[14,33]. ROS are produced through a Fenton-type reaction as follows:

$$LCu(II)+H2O2 \longrightarrow LCu(I) + \bullet OOH+ H+$$

$$LCu(I)+H2O2 \longrightarrow LCu(II) + \bullet OH + OH-$$

where L = organic ligand. Similar to Cu toxicity, Cu deficiency also affects, directly or indirectly, the components of the oxidant defense system and as a result increased ROS and oxidative damage to lipid, DNA, and proteins have been observed in human cell culture models or clinical syndromes of severe copper deficiency[18,20]. Copper could act as a "double-edged sword" by inducing DNA damage and also by inhibiting their repair [4]. Additionally, copper can bind directly to free thiols of cysteines resulting in oxidation and subsequent crosslinks between proteins leading to impaired activity [33].

ACERULOPLASMINEMIA: Ceruloplasmin is a copper containing glycoprotein produced in the liver that binds about 95% of the copper in serum. This glycoprotein presents ferroxidase activity and catalyzes the conversion of ferrous to ferric iron which is then transferred to transferrin [19]. A total absence of circulating serum ceruloplasmin (aceruloplasminemia) could lead to ferrous iron abundance within both the reticuloendothelial system and parenchymal cells, It is noteworthy that hereditary ceruloplasmin deficiency (or aceruloplasminemia) is an autosomal recessive disorder altering iron metabolism [34]. It is accompanied by mutations of the ceruloplasmin allele on chromosome 3q.Manifestations of aceruloplasminemia at the clinical level are diabetes mellitus, retinal pigmentary degeneration, dystonia, extrapyramidal signs, cerebellar ataxia, and dementia. Histopathologic studies have presented significant agglomeration of iron in the liver, pancreas, retina, and central nervous system[35,36]. Although the pathogenesis of brain damage in aceruloplasminemia is currently not fully understood, it is well recognized that iron-mediated oxidative stress could be implicated in neuronal cell death[37,38].

WILSON'S DISEASE**:**Wilson's disease is an autosomal recessive disease of copper metabolism of which the primary genetic defect is in ATP7B gene [1,9]. The biological role of ATP7B gene is to encode a copper-transport protein located

at the trans-Golgi network and to transfer Copper into the secretory pathway for both annexation into ceruloplasmin and excretion into the bile [39]. A major contribution to pathophysiology of Wilson's disease is Cu-mediated oxidative damage, activation of cell death pathways, and eventual leakage of copper into the plasma pool, which ultimately results in the accumulation of excess copper in extrahepatic tissues [5]. Notably, the hepatic Copper overload associated with Wilson's disease is histopathologically characterized by bulgy hepatocytes, inflammation, and cytoskeletal alterations and finally leads to cirrhosis. Wilson's disease presents severe neurological symptoms, but when it is diagnosed in time, it can be treated with several ways including the use of chelating agents, low-Cu diets, and high levels of Zn supplements [40,41].

THE MENKES DISEASE:The Menkes disease is an Xlinked recessive disorder caused by defects in a gene that encodes a copper-transporting ATPase (ATP7A) [19,20]. A gene product functions as an intracellular pump to transport copper into the trans-Golgi network for incorporation into copper-requiring enzymes including dopamine-β-hydroxylase (DBH) and also mediates copper exodus from cells. Copper uptake and excretion by the liver are normal in Menkesdisease as well as copper enzyme levels, but the absorption of copper in the gastrointestinal tract is severely impaired [42]. The significantly decreased intestinal absorption of copper results in a shortage of exchangeable copper followed by a deficiency of cuproenzymes with important role in the developmental level [43]. It should be emphasized that the uptake by peripheral tissues is normal; however, excretion and intracellular copper trafficking are disrupted by mutations in the ATP7A gene. As a result of impaired copper efflux, peripheral tissues in MD patients tend to accumulate copper in the form of copper metallothionein. At the clinical level, MD is characterized by progressive neurological impairment and death in infancy. Because of the block in intestinal absorption of copper, the major clinical impact is from copper deficiency in the brain of the developing fetus, leading to severe brain damage [34].

ULCER: The formation of copper complexes of non-steroidal anti-inflammatory drugs **(NSAID)** not only markedly improved their anti-inflammatory effect, but also eliminated their principal toxicity, ulcerogenicity, and produced compounds with very potent antiulcer activity in models of gastric and intestinal ulcer [44]. Since it is well known that clinically used anti-arthritic drugs cause ulcers and gastrointestinal distress, the observation that copper complexes have antiulcer activity further distinguishes these compounds from their parent ligands as being safer and potentially much more therapeutically useful [6]. From the results of Copper complexes studied to date, it seems to be true that nearly all copper-containing compounds are orally effective antiulcer agents. Although some are more potent than others, these relative potencies may depend upon the model of ulcer used. There is generally good agreement in comparisons of results obtained by various investigators. Some, however, have found gastric irritation using inappropriate mixtures of NSAIDs and inorganic copper salts or inappropriate interpretations of their experimental data [26,28].The lack of gastric irritation, the presence of antiulcer activity, and the enhanced anti-inflammatory activity of these complexes make this class of potentially useful antiarthritic drugs particularly promising, since the arthritic syndrome is likely to include gastric ulcers [30].

INFLAMMATION: Continued interest in copper complexes as anti-inflammatory agents and their potential as antiarthritic drugs is evidenced by the number of reviews and symposia proceedings published recently [4,9,26,45]. This selection contains both an historical and an updated review of studies of copper metal, inorganic compounds, and complexes as anti-inflammatory agents. Before 1969, occasional publications reported that sodium 3-(N-allylcuprothioured0)- 1-benzoate and cuprous [28,29] in various models of inflammation and fever. In the nineteenth century Perrin (1965) and William (1972) reported that cupric carbonate (Cu(OH), CuCO,) and cupric complexes of acetic, lauric, oleic, caprylic, butyric, sebasic, lipoic and cinnamic acids were also effective in animal models of inflammation. Ceruloplasmin acts as an acute-phase reactive protein to stress and trauma conditions. As a consequence, elevated copper concentrations have been found in response to inflammation, infection, and various chronic diseases, such as arthritis. Serum copper levels are higher than normal in varied inflammatory diseases in humans [46]. The higher levels of ceruloplasmin are accountable for the increased serum copper in the preceding conditions. Moreover, the anti-inflammatory results of copper have been shown in humans. On the other hand, the acute or chronic inflammation actuates changes on the metabolism of copper, which contribute to altered serum and tissue levels. The increase of serum copper in inflammation could be due to the increase of ceruloplasmin, which is an acute-phase protein [39,47].

CANCER: Copper metabolism has been studied in a variety of neoplastic diseases [23]**.** It is now known that patients with acute leukaemia have elevated serum or plasma copper concentrations [48]**.** The elevation in serum copper correlated with an increase in number of bone marrow blast cells. Adecline in symptoms or remission of disease following therapy correlated with a decrease in serum copper concentration**,** enabling accurate prognoses based upon serum copper determinations. Inorganic copper was also found to be effective in preventing ethionine induced liver tumours in rodents and a variety of other animal carcinomas [3,45].

However, treatment with inorganic copper was not as effective as therapy with copper complexes. Asingle 5 mg/kg dose of Cu(II)(dimethylglyoxime), increased the life-span of mice bearing Ehrlich ascites or Sarcoma 180 tumours 2- to 3-times that of non-treated controls[44]. Other copper complexes reported to have similar antitumour activities in rodents are Cu(II)(3,4,7,8,-tetramethyl-1,lO-phenanthroline): + (Ottet.,al 2007), Cu(II)(2-keto-3-ethoxybutyraldehydebisthiosemicarbazone) [67,68,69], Cu(II)(pyruvaldehydebisthiosemicarbazone) (Coluccia 2007), copper complexes of 2-formylpyridine and 1 -formylisoquinolinethiosemicarbozones[34,44], copper-bleomycin,

Cu(II)(glycylglycylhistidinate),Cu(II)(glycylhistidyllysine), Cu(II)(pyridine-2-carboxaldehyde-2-pyridylhydr~onate), Cu(II)(salicylaldehydebenzoylhydrazonate), Cu(I1) amino acid, Cu(II)(2,3,4- trihydroxybenzaldoximate), and a large variety of other classes of copper complexes[22][4]. In addition to demonstrating antitumour activity for these copper complexes, mechanistic studies provided a great deal of information concerning their possible inhibition of DNAsynthesis [13].

Recently, it was shown that copper proteins are associated with metabolic changes in cancer cells and most importantly play a significant role in angiogenesis by stimulating proliferation and migration of human endothelial cells [27]

CHEMICAL STUDIES OF BIOLOGICALLY RELEVANT COPPER COMPLEXES

Perrin (1965), Williams(1972),May and Linder (1977), Berthon (1986) and their colleagues developed computer models to study complex formation between low- and high-molecular-weight ligands, such as amino acids, drugs and plasma peptides, and a variety of essential metalloelements, including copper. With their models, they have been able to list possible complexes of copper present in blood, the relative amounts of each, and those responsible for tissue distribution and excretion of copper. Recent Computer modelling has also provide experimental evidence in support of hypotheses that the administration of low-molecular-weight complexes would be beneficial in the treatment of arthritic, ulcer, infections and epileptic diseases [46]. Aiming at the synthesis of potent anticancer drugs, binuclear copper(II) complexes of pyridyl-diamines, as well as mixed-ligand acetylacetone/quinoxaline complexes exhibiting nuclease and apoptosis-inducing activity, have been reported recently [47,48]. In addition the antitumor activity of Schiff-base copper(II) complexes has been investigated[49]. The evaluation of a new thiosemicarbazoneCu(II) chelate was reported to induce tumor growth inhibition both *in vitro* and *in vivo*, through oxidative/endoplasmic reticulum stress[48]

Studies of the physicochemical requirements for bonding of antiarthritic drugs with copper-albumin, a loosely bonded form of copper in human blood, demonstrated copper release and the formation of pharmacoactive forms of these drugs [50]. Studies of copper and albumin bonding demonstrated that metalloelements are bonded to this peptide and support the generally accepted view that albumin complexes are transportation forms of metalloelements[41]. Results of studies relevant to cupresis in arthritis patients given penicillamine suggest that this drug increases the amount of exchangeable copper in plasma by liberating copper from metalloproteins, which was then instrumental in controlling inflammation [44,50]. Stabilities of copper complexes of salicylic and acetylsalicylic acids were determined to estimate their concentrations in tissues as they pass through the body. It was concluded that the Cu(II)(salicylate), complex was more absorbable and that the complex dissociated at some point in the process of causing anti-inflammatory and antiulcer effects [43]. It was suggested that all effective copper complexes, including copper complexes of antibiotics, were able to pass through membranes and facilitate tissue distribution of copper [41,44]. Metalloprotease activity of the complex 2,6-bis(benzimidazo- 2-yl)pyridine copper (II) chloride was found with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) with bovine serum albumin in the presence of oxygen. Albumin undergoes site-specific cleavage with the resultant formation of four fragments of molecular weight 49, 45, 22 and 17 kDa Bridged Cu(II) complexes of 6-(methoxybenzylamino)purines show antioxidant activity both *in vitro* and *in vivo.* Values of IC50 = 0.253 up to 1.250 μM were reported for the superoxide-dismutase- (SOD-)mimic activity for the Cu complex *in vitro* compared to IC50 = 0.480 μM of the native bovine Cu,Zn-SOD enzyme, used as a standard. The pretreatment of mice with Cu complexes *in vivo* led to the complete elimination of cytotoxic attack of alloxan-induced *diabetes* and its free radical metabolites (cytoprotective effect)[49]. Copper complexes that exhibit high SOD-like activity are potent drugs for prion diseases since such activity is correlated with antisprion activity. It is known that prion proteins can bind Cu(II) ions with high specificity as they possess a number of copper sites. Moreover, in the development of prion disease, copper may modulate the rate of protein misfolding[50].

IV. CONCLUSIONS

Developing an integrated picture for the role of copper and its complexes in medicine is a challenging task that awaits further exploration. Copper ions are considered as multifunctional participating in a broad spectrum of intracellular processes under normal and pathologic conditions. However, many questions remain unanswered. Further experimental and clinical studies would aid at unraveling their prominent activities. Copper complexes described in the present work show a diverse *in vitro* biological activity, ranging from antibacterial and anti-inflammatory to cytostatic and enzyme inhibitory. At molecular level such complexes interact directly with proteins and DNA, leading to dysfunction and cleavage of the macromolecular structure, or indirectly producing ROS that attack and degrade biomolecules. Since DNA is a potent target of cytostatic drugs, the effect of copper compounds on DNA functionality is very important. The ability of Cu(II) complexes to bind to DNA and exhibit nuclease activity in the presence of reducing agents is well established (Wang et., al 2010). DNA degradation is believed to take place through a Fenton-type reaction in which ROS are produced. The type of organic ligands in such copper complexes seems to affect and regulate their activity. The effect of ligand chelation may also be of importance for the biological activity of the complexes, whose exact role has not been elucidated yet. Spatial geometry of the complex and the structure of the ligand influence to a lesser extent the activity of the complex. The biological activity of the ligand is usually increased upon complex formation, but evidence of a synergic effect between the metal and the organic ligand is still lacking. In conclusion,

novel treatment options that interfere with copper complexes have been proposed in experimental systems, albeit their effectiveness in clinical practice remains to be further investigated. The great pressure for producing new effective treatment options in medicine should not surpass the necessity for careful, rationally designed randomized studies evaluating the most promising copper complexes as therapeutic pharmaceuticals.

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