Biological Importance of Copper and Zinc Metal Complexes

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ABSTRACT: The purpose to write this review article is to analyse the biological activities of Copper and Zinc metal complexes. Copper and Zinc metal complexes play an essential role in development of new metal based drugs. The data has drawn from randomly selected research papers which have been published in last few years. In this article, we have discussed about Cu (II) and Zn (II) metal ions which form complexes with various ligands such as heterocyclic ligands, Schiff base ligands and terpinoids etc. and their biological importance. In this article, we took applications of metal complexes in the area of antifungal, antitumor, antibacterial, anti-inflammatory, antimicrobial activities.

Keywords - Copper and Zinc metal complexes, Biological activities, Schiff base ligands, Heterocyclic ligands

1. INTRODUCTION

Copper is one of the few metals that is present in nature in a directly usable metallic form. Copper is a member of the first transition series of elements, which consists of Scandium, Titanium, Vanadium, Chromium, Manganese, Iron, Cobalt, Nickel, Copper and Zinc and belongs to group 11 of the periodic table, ahead with silver and gold. The element has an atomic number 29, an atomic mass and 63, two main oxidation states +1 and +2. The electronic configuration of copper is $[Ar]3d^{10}4s^1$. Copper complexes are reddish orange in colour and $[Cu(H_2O)_6]^{2+}$ are blue in colour. Copper complexes show paramagnetic behaviour[1]. Copper ion has very high melting and boiling points. Copper metal complexes usually have octahedral geometry. The tendency of Cu to change into Cu^{2+} ions is extremely low due to its negative electrode potential[2]. It is a soft, malleable, and ductile metal with very high thermal and electrical conductivity.

Copper metal ion makes complexes with different type of ligands In aqueous solution, copper (II) exists as $[Cu(H_2O)_6]^{2+}$ and other copper metal complexes exist as copper(II) acetate, copper(II) nitrate, and copper(II) carbonate. Copper (II) sulphate forms a blue crystalline pentahydrate, the most familiar copper compound in the laboratory[3]. It is used in a fungicide called the Bordeaux mixture. There are three types of copper metal complexes i.e. Cu(III), Cu(II) and Cu(I), but very few examples of copper(III) compounds are available. Copper (II) complexes play an important role in the active sites of a large number of metalloproteins in biological systems and potential application for numerous catalytic processes in living organisms that involve electron transfer reactions or activation of some antitumor substances. Copper metal complexes have been found to interact with biological systems and to exhibit antineoplastic, antibacterial, antifungal and anticancer activities[4].

Copper metal complexes possess an important role in the designing of metal-based drugs. These complexes are more effective against infectious diseases compared to the uncomplexed drugs. The copper(II) ion which has proved beneficial in many diseases such as tuberculosis, gastric ulcers, rheumatoid arthritis, and cancers[5]. Some copper metal complexes are good anti-cancer agent. Copper metal based antitumor drugs play important role in antiblastic chemotherapy.

Zinc metal complexes are the chemical compounds containing the elemental zinc, which is a member of group 12 in periodic table. The oxidation state of most of the compounds is +2. Generally zinc complexes have Zn^{+2} ions, with an electronic configuration $[Ar]4s^23d^{10}$ and radius 0.65 Å. Zinc is strong reducing agent and the value of its standard redox potential is −0.76 V. As such its complexes have tendency to be symmetrical. Zinc complexes are kinetically labile. i.e. the Zn-ligand bonds exchange with other ligands rapidly. For this reason, zinc ions are at the catalytic centres in many enzymes. Complexes with zinc in the oxidation state +1 are extremely rare. No compounds of zinc in oxidation states other than +1 or +2 are known[6]. Calculations indicate that a zinc compounds with the oxidation state +4 is unlikely to exist. Zinc complexes are mostly colourless. Exceptions occur when the compound contains a coloured anion or ligand. Zinc complexes are typically diamagnetic, except in cases where the ligand is radical. Zinc metal complexes are biological active compounds. The structure of zinc metal complexes is tetrahedral. In such a geometry, ligands clearly attach with zinc metal ion and obey the octet rule. Zinc metal complexes having tetrahedral structure are mostly found in metallo-enzymes. The example is carbonic anhydrase. They are also found in many proteins.[7]

The transition metals complexes iron, copper, cobalt, nickel, zinc etc. metals with variety of ligands have proved their excellent biological activities. The transition metals have nature of losing of electron and convert to a positively charged ion. This nature of metal complexes allows metals to play an important role in biological activity. In metal complexes, the metal ion is electron deficient and most of biological molecules like proteins and DNA molecules are electron rich molecules. Attraction of these opposite force leads to a general tendency for metal ions react or interact with different types of biological molecules.[8] Zinc metal complexes which are having Zn^{+2} ion are important in biological system and play important role in activity of nearly 300 enzymes and 50 important cellular biochemical reactions.[9]

Zinc metal makes different complexes with different ligand and play essential role in biological activity such as Antibacterial, Antifungal, Antileukemia etc. activities. [10]

The main purpose of this literature review is, to study the biological activities of copper and zinc metal complexes during the last few years

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2. Biological activity

Biological activity is defined as,"It is the term which describes the benefits and side effects of medicines or drug on a living matter." Biological activity is also known as pharmacological activity. [11]

Biological activity or Pharmacological activity plays an important role in uses of compounds in the medical applications.

3. Biological activity of copper metal complexes

Many drugs possess modified toxicological and pharmacological properties in the form of metal complexes. Copper metal complexes have been used as a result of their varied biological properties which include antibacterial, anticoagulants, antibiotic, antifungal, anticancer, and anti-inflammatory. Copper is a bio-essential and bio-relevant element in biological activity. The activity of bio metals is attained through the formation of complexes with different bio ligands and the mode of biological action for complexes depends upon the thermodynamic and kinetic properties. Interaction of various metal ions with antibiotics may enhance their antimicrobial activity as compared to that of free ligands.

Copper is incorporated into a number of metalloenzymes involved in haemoglobin [12]. Copper metal complex play important role in our metabolism. In our human body, One of the most common trace-metal imbalances is elevated copper and zinc. Copper metal is present in every tissue of the body, but is stored primarily in the liver, with fewer amounts found in the brain, heart, kidney, and muscles. Copper is essential for maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body. Copper metal complexes can acts as both antioxidant and pro-oxidant. Copper metal acts as a anti-oxidant ligand which damage cell walls and interact with genetic material ,and for the development of a number of health problems and diseases, and as pro-oxidant ligand neutralize free radicals and may reduce or help prevent some of the damage they cause[13,14]

Tetradentate Schiff base ligands are derived from Knoevenagel condensation. For example, β-ketoanilides, furfural with o-phenylenediamine and diethylmalonate and their Cu (II) complexes showed antibacterial activity against Escherichia coli, Salmonella typhi, Staphylococcus aureus, Klebsiella pneumonia. The complexes have higher antibacterial activity than that of free ligand [15]. Schiff base ligand such as 2-acetylpyridine thiosemicarbazones and their copper complexes possess significant antimalarial activities and their copper (II) complex has showed anti-malarial activity against malaria parasite, Plasmodium falciparum. Cu (II) complexes have shown better antifungal activity compared to the ligand and the metal salts. Copper Metal complexes of Schiff's base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid have show, anticancer activity and their metal complex has proteasome inhibitory activity in human breast cancer and leukaemia cells[16].

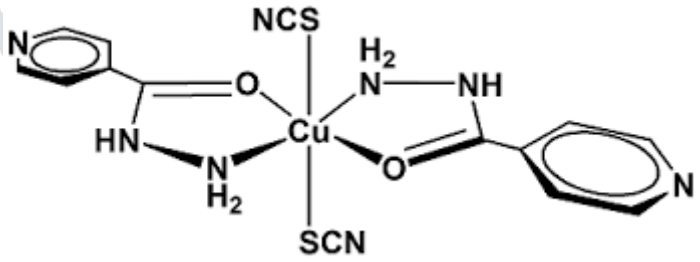
Study of antibacterial and antifungal activity using Cu (II) complexes with the salicylidene thiosemicarbazones (H_2L_1–H_2L_{10}), obtained from the condensation reaction of thiosemicarbazones or 4-phenylthiosemicarbazide with 2-hydroxybenzaldehyde derivatives has been porformed. This reaction give a three copper metal complexes $C_{18}H_{17}Br_2CuN_7O_3S_3$, $C_8H_{12}Br_2CuN_4O_3S$, $C_{18}H_{19}CuN_7O_3S_3$. All copper metal complexes show their antibacterial activity against Staphylococcus aureus (Wood-46, Smith, 209-P), Staphylococcus saprophyticus, Streptococcus (group A), Enterococcus faecalis (Gram-positive), Escherichia coli (O-111), Salmonella typhimurium, Salmonella enteritidis, Klebsiella pneumoniaie, Pseudomonas aeruginosa, Proteus vulgaris and Proteus mirabilis (Gram-negative) and show their antifungal activity against aspergillus niger, Aspergillus fumigatus, Candida albicans and Penicillium strains[17].

Copper (II) metal complexes give two mononuclear pentacoordinated complexes formulated as--(1) [Cu(L)(Br)(H_2O)] and (2) HL= (1-[(3-methyl-pyridine-2-ylimino)-methyl]-naphthalen-2-ol). These types of copper (II) chelates have been interacted with biological systems and showed their antineoplastic activity, antibacterial,

antifungal and anticancer activity. Some copper(II) N,S,O/N,N donor chelators are good anticancer agents because of having strong binding ability with DNA base pair**.** Biological activity of copper (II) complexes depends on the impermeability of the cell of the microbes or difference in ribosome of microbial cells. However, the activity increases with increasing concentration of complexes. These copper (II) complexes exhibit higher antibacterial activity than their free ligands.

Cu (II) complexes binding with Thiosemicarbazones as a ligand show good anticancer chemotherapeutic property. Cu (II) metal complexes of thiosemicarbazones show increase biological activities such as antibacterial, antifungal, anti HIV, and anti-inflammatory [18]. The in vitro antibacterial activity of thiosemicarbazones and their metal complexes was assayed by the disk diffusion method using cultures of S. aureus, S. pyogenes, S. typhimurium and E. coli. Cu (II) complexes $C_{18}H_{26}N_6S_2CuCl_2$ and $C_{22}H_{32}N_6S_2O_4$ Cu show good biological activity as compare to Co(II) metal complexes.

Metal complexes with a variety of organic chelating ligands show good biological activities. Three metal complexes with bonding of salicylic acid and heterocyclic ligands (1) ([$Cu(H_2O)$(5-Cl-Sal)(Neo)] (2) [Cu(μ-Sal)(Neo)]$_2$, (3)Cu_2(μ-5-Cl-Sal)(5-Cl-HSal)$_2$(Neo)$_2$]·EtOH and these are all compounds biological active [19]. Biological activity of copper metal complex of (4), [$Cu(NCS)_2(INH)_2$].$5H_2O$ (5) and [$Cu(NCO)_2(INH)_2$].$4H_2O$ Both metal complex are derivate of [$CuCl_2(INH)_2$].H_2O. This complex shows best Mycobacterium tuberculosis (MTB) activity and also increasing the antimicrobial activity against Staphylococcus aureus and Escherichia coli (Structure 1)[20]. The antitubercular activity of the compounds was determined by the REMA methodology as described by Palomino and colleagues [21].



Structure 1 [Cu(NCO)2(INH)2].4H2O

Habala et.al studied the formation of copper metal complexes with six type of Schiff base ligand. The ligands are: (1)N[[(4(trifluoromethyl)phenyl]methylidene]pyridine4carbohydrazide (2)N[[(2trifluoromethyl)pheyl]methylidene]pyridine4carbohydrazide(3)N[(4fluorophenyl)methylidene]pyridine-4-carbohydrazide monohydrate (4) N-[(5-fluoro-2-hydroxyphenyl)methylidene]pyridine-4-carbohydrazide (5) N-[(3-fluoro-2-hydroxyphenyl)methylidene]pyridine-4-carbohydrazide (6) N-(benzylidene)pyridine-4-carbohydrazide[22,23]. Their general formula is [Cu (Ln-H) $_2$][24]. Two Schiff bases (1 and 4) have shown significant activity against C. albicans. The Schiff base L4 exhibited weak activity against E. coli. Among the copper (II) complexes, only Cu-L6 showed any noteworthy activity against aureus[25]. In the two ligands containing hydroxyl (4 and 5), the Schiff base with fluoro substituent in para position to the hydroxyl group have shown significantly higher activity than with the same group in the ortho position [26]. All six copper (II) complexes show excellent inhibition of Jack bean urease [27].

The compound of cu(II) ion and tridentate ligands such as [Cu(SPF)(L^n)Cl] where SPF is sparfloxacin and L^n= substituted terpyridines their work against microorganisms like Escherichia coli, Pseudomonas aeruginosa[28]. The copper(II) complexes with NS donor ligand show their antibacterial property against gram(+ve) and gram(-ve bacterial)[29-30]. The complexes of N,O-donor ligand and ciprofloxacin with Cu(II) ion show their antibacterial activity against Bacillus subtillis, Escherichia coli bacteria(Patel et.al)[31].

Biological Activity of Zinc Metal Complexes

Zinc is a very essential compound in biological system. It plays a key role in variety of metabolic pathways, cell differentiation, apoptosis and proteins stability [32]. Zinc metal ion makes various complexes with different types of ligands such as heterocyclic ligands, Schiff base ligands etc. These complexes are also important in modern medical science. Zinc metal complexes have been characterized spectrophotometrically and biological activities have been determined. The heterocyclic ligands and their Zn (II) complexes have been screened against bacteria (gram-positive or gram-negative) to assess their growth inhibitory potential as antibacterial agents.

Zinc plays a vital role in wound healing, proper functioning of mucosal cells, reduction of reactive oxygen species (ROS) [33] Zinc is a cofactor for metallo-enzymes [34] Complexes of zinc ions and certain Schiff base ligands has

been studied due to their specific property in bio inorganic chemistry i.e. carbon-oxygen bond or different types of bond. [35] These complexes are important in many enzymatic reactions. [36] Zn(II) ion form a complexes with Schiff bases derived from piperazine compounds have been described to demonstrate various biological activities like anthelmintic [37] antimicrobial [38] anti-HIV [39] etc.

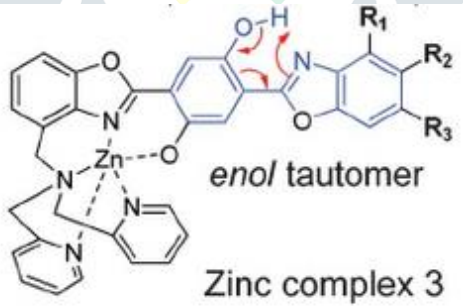
Zn (II) complexes with β-diketonates having metal oxygen bond, play a pivotal role as a structural cofactor in metalloproteins. However, they act as preventers of HIV-1. [40] Additionally, Zn (II) ions are present in most of DNA and RNA polymerases. [41]

Biological activities of Zn (II) porphyrin complexes have been also found. The general formula of these complexes is [X-Zn-t(*p*-CH_3) PP] [where X = different phenolates as axial ligand]. These complexes show antifungal activities against "Sclerotium rolfsi [42].

Metal complexes of Zn (II) [$Zn(ISO)_2$] and [$Zn(BUT)_2$] of the polyhydroxychalcones show antioxidant activities. [43] Zinc and rifampicin complex show antimycobacterial activity as compare to free RIF complex and zinc complex. Zn-R IF complex work as antibacterial agent against M. smegmatis and M. bovis bacteria. These types of complexes also kill mycobacteria residing inside macrophages. They fight against intracellular pathogen by entering the cell and kill the bacteria. [44]

Five co-ordinate Zn (II) complexes show antibacterial activities. These type of complexes with hydrazine Schiff base exhibit low antibacterial activities when its concentration is >800 ppm by disc diffusion method. [45] Zinc and Schiff base complex prevent the cancer progression in both in vivo and in vitro by inducing apoptosis. These types of complexes are less toxic and potent anticancer agent, zinc atom is attached with suitable cysteine-base. These complexes are a very well chemotherapeutic agent and it work against specifically targeted maligent cells and multidrug resistance in cancer without any side effect. [46] Zinc complexes derived from an asymmetric bidentate Schiff base ligand. They exhibit the effect of the metal ion on the binding of the complexes to DNA. Zinc based complexes inhibit the growth of liver cancer cells. These types of complexes are synthesized under solvothemal conditions. Example, $\{(H_2NMe_2)_2[Zn_3(BTB)_2(OH)(Im)](DMF)_9(MeOH)_7\}n$ where BTB=1,3,5-benzenetrisbenzoicacid, Im=imidazole, DMF=N,N-dimethylformamide [47].

Zn (II) ion forms the complex with dipicolylamine which is known as zinc (II)-dipicolylamine complexes (ZnDPA). ZnDPA complexes show antiplasmodial activity against three strains of Plasmodium Falcipuram, which is the cause of malaria. They also work as antimalarial agents. [48] Zinc metal with imidazole based ligands L1=2-p-tolyl-(1H-imidazo[4,5-f][1,10] phenanthroline), L2=2-p-chloro-benzene-(1H-imidazo[4,5-f][1,10]phenanthroline), L3=2-(3-indole)-(1H-imidazo [4,5-f][1,10]phenanthroline), L4=2-(3-7-azaindole)-(1H-imidazo[4,5-f][1,10]phenanthroline) obtained from multi component reaction. The newly synthesized complexes have biological efficiency and they work against growth of bacteria and fungi in vitro to evaluate their antimicrobial potential. [49] Zn (II) complex with Benzoxazole base acts as a multidrug resistance in cancer. Such of complex not only act as MDR agent, but also as a apoptosis inducers (Structure 2) [50].



Structure 2 Benzoxazole Based Zn (II) Complex

Complexes of Zinc (II) with heterocyclic ligands act as antimicrobial agents. Antimicrobial activity of Schiff base ligand and their metal complexes have been studied against gram-positive and gram-negative bacteria. Some complexes show perfect antifungal activity.$[Zn(NMAPIMHMC)_2]\cdot 2H_2O$, $[Zn(TMPIMP)_2]\cdot 2H_2O$ and $[Zn(HBABO)_2]\cdot 2H_2O$ against C. albicans and A. niger. [51]

Zinc metal makes complexes with Thiosemicarbazones ligands which have received considerable attention because of their antibacterial, antifungal, antitumor, ant amoebic, antimalarial, antiviral, radio protective, trypanocidal, and anti-inflammatory activities.[52-53] The antifungal activity of the ligand and its metal complexes were tested against pathogenic fungi, Candida albicans and Aspergillus niger.[54-55] Zn(II) diethyldithiocarbamate complexes play an essiential role against proteasome in breast cancer cells. It is discovered by Boris Cvek et. al. [56]

CONCLUSION

Cu (II) and Zn (II) complexes have been much of interest over the last few years widely because of its various applications in biological processes. The findings of this review article confirm the importance of ligand complexation with copper and zinc metal ion. It shows that, biological importance of Cu (II) and Zn (II) meta complexes varies different types of ligands attached with them.

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