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Transition metal complexes and their application in drugs and cosmetics – A Review

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ABSTRACT

Inorganic compounds particularly transition metals have played an important role in the development of new metal based drugs and in some cosmetic formulations. In this review a cursory look at the application of these metal complexes in the areas of pharmacy, microbiology and cosmetology has been expatiated to provide an insight of the contribution of inorganic chemistry towards drugs and cosmetic delivery.

Keywords: Metal complexes, pharmaceuticals, cosmetics.

INTRODUCTION

Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands. (Cox, 2005). Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This ctivity of transition metals has started the development of metal based drugs with promising pharmacological application and may offer unique therapeutic opportunities. (Rafique *et al.*, 2010). The advances in inorganic chemistry provide better opportunities to use metal complexes as therapeutic agents. The mode of action of metal complexes on living organism is differing from non metals. These complexes show a great diversity in action.(Hariprasath *et al.*,2010). Medicinal inorganic chemistry can exploit the unique properties of metal ions for the design of new drugs. This has, for instance, led to the clinical application of chemotherapeutic agents for cancer treatment, such as cisplatin.(Pieter *et al.*, 2008) The use of transition metal complexes as therapeutic compounds has become more and more pronounced. These complexes offer a great

diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti diabetic compounds. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that is, unimaginable in few years back. (Rafique *et al.*, 2010). Transition metal complexes are important in catalysis, materials synthesis, photochemistry, and biological systems. They display diverse chemical, optical and magnetic properties. This review is aim at having an insight on the modern application of transition metal complexes in the production of drugs and cosmetics, with a critical overview of the present advancement in these areas.

Antibiotics as inhibitors of some metal complexes.

Antibiotics are substances which, even at low concentrations, inhibit the growth and reproduction of bacteria and fungi. The treatment of infectious diseases would be inconceivable today without antibiotics. (Koolman and Roehm, 2005)

Most of the antibiotics were originally derived from micro-organisms while the chemotherapeutic agents are from plants.(Chhetri *et al.*, 2010)

Several antibiotics, such as **antimycin A** and **myxothiazol,** inhibit the electron transport by the cyt-*b*/*c*1 complex. Due to its positive charge, reduced cyt-*c* diffuses along the negatively charged surface of the inner membrane to the **cyt-a/a3 complex** (Fig.1), also termed **complex IV** or **cytochrome oxidase**. The cyt-*a*/*a*3 complex contains 13 different subunits, three of which are encoded in the mitochondria.

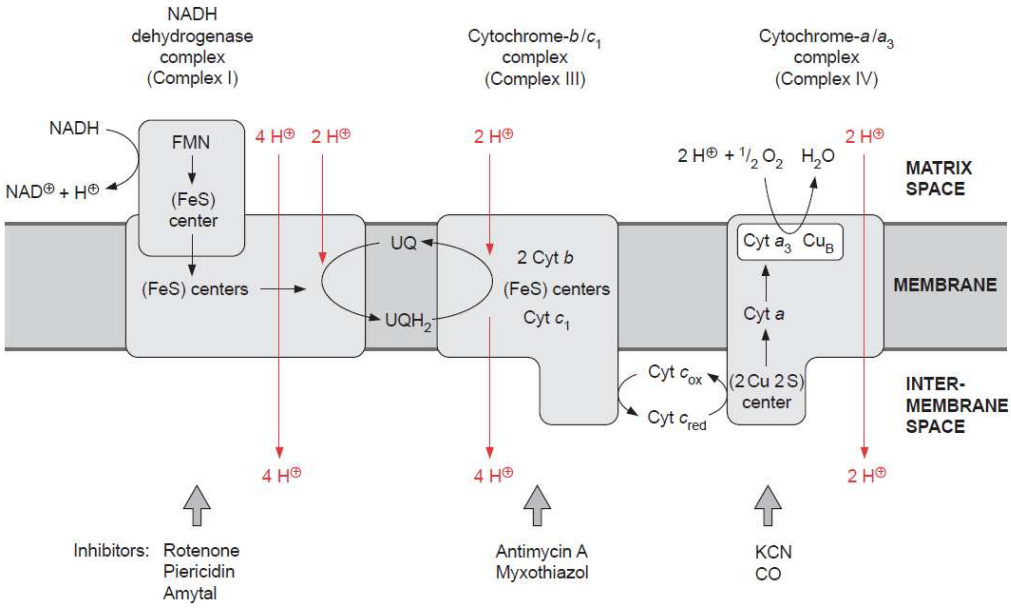

Figure .1 Scheme of the location of the respiratory chain complexes I, III, and IV in the mitochondrial inner membrane. (Heldt and Heldt, 2005)

Recently the three-dimensional structure of the cyt-*a*/*a*3 complex has been resolved by X-ray structure analysis of these complexes from beef heart mitochondria and from *Paracoccus denitrificans*. The complex has a large hydrophilic region that protrudes into the intermembrane space and contains the binding site for cyt-*c*. In the oxidation of cyt-*c*, the electrons are transferred to a **copper sulfur cluster** containing two Cu atoms called CuA. These two Cu atoms are linked by two S-atoms of cysteine side chains (Fig. 2). This copper-sulfur cluster probably takes up one electron and transfers it via cyt-*a* to a **binuclear center**, consisting of cyt-*a*3 and a Cu atom (CuB), bound to histidine. This binuclear center functions as a redox unit in which the Fe-atom of the cyt-*a*3, together with CuB, take up two electrons. $[Fe^{+++}.Cu_B^{++}]+ 2e^- \rightarrow [Fe^{++}.Cu^{+}_B]$

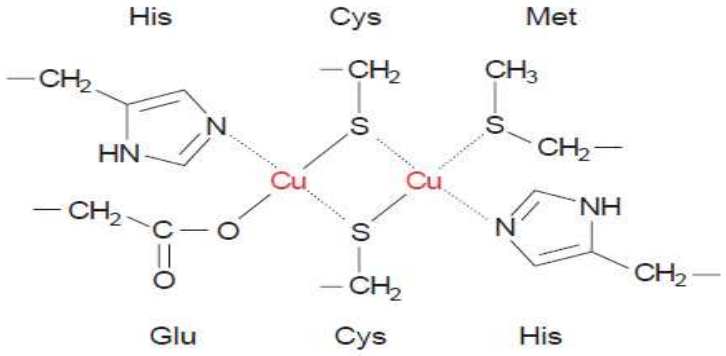

Fig.2.Copper sulfur cluster of the cytochrome-*a*/*a*3 complex, termed CuA, a Cu2+-and a Cu+-ion (Heldt and Heldt, 2005).

Anti-microbial assay

Biological activity of the ligand and a series of its metal complexes [Cu(II), Ni(II), Co(II) and Mn(II)] were screened for antibacterial activity against S.sureus as gram positive bacteria and E.coli as Gram-negative and the fungi A. fumigatus by Jayaseelan, *et al*, (2010) using broth micro dilution procedures. From Table1, the Gram positive bacteria on all metal complexes were found to inhibit all tested bacteria at different rates and the activity as following order Co > Ni > Cu > Mn. In Gram negative bacteria also follows the same order and all complexes have higher bacterial activity than ligand. In fungal activity, the ligand showed activity against Aspergillus fumigatus and metal complexes show activity in the following order Cu > Co > Ni >Mn. It is known that chelation tends to make the ligand to act as more powerful and potent bacterial agent. A possible explanation for this increase in the activity upon chelation is that, in chelated complex, positive charge of the metal is partially shared with donor atoms present on ligands and there is an electron delocalization over the whole chelating ring. This, in turn, increases the lipid layers of the bacterial membranes.

Table-1: Anti-microbial Activities of Ligand and Metal Complexes (Jayaseelan *et al.*, 2010)

Sample	Bacteria						Fungi		
	Gram-positive			Gram-negative					
	S.aureus			E.Coli			A.Fumigatus		
	50 µg/mL	100 µg/mL	150 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL
Ligand	4	10	13	5	9	12	4	11	13
$[Cu_2(L)(NO_3)_4]$	10	13	18	11	15	17	12	15	19
$[Ni_2(L)]^{4+}4Ac^-$	9	11	16	10	14	15	12	14	17
$[Co_2(L)(NO_3)_4]$	11	13	19	13	16	19	11	14	18
$[Mn_2(L)Cl_4]$	8	10	15	9	14	15	10	15	19

Antibacterial activity of metal complexes

Air stable Ag(I), Co(II) and Cu(II) complexes of pyrimethamine have been synthesized and characterized by Idemudia and Ajibade (2010) Based on their electronic spectral results, a linear geometry has been suggested for the Ag(I) complexes, tetrahedral geometry and an octahedral geometry for Co(II) and Cu(II) complexes. The antimicrobial screening of the complexes showed that the Ag(I) complexes have enhanced activity, with {[Ag2(pyrm)2].0.7CH3OH} showing a stronger antimicrobial potential at an MIC value of 0.03125 mg/ml.(Idemudia and Ajibade ,2010)

Antimicrobial test

Selectivity test of metal complexes on bacteria isolates revealed that the silver complexes possess antimicrobial activities compared to the pyrimethamine drug which did not show any activity. The Ag(I) complexes exhibited activities against all eight bacterial isolates comprising of both gram-positive and gram-negative organisms. These showed that the Ag(I) complexes possess a broad spectrum activity. *P. vulgaris* shows the least zone of inhibition with 7.5 mm and 12.5 mm in [Ag(pyrm)2 Cl]_3H2O and [Ag(pyrm)CH3COO] respectively. While Staphylococcus *aureus* has the highest zone of inhibition with 20.5 mm and 22 mm for [Ag(pyrm)2Cl]_3H2O and [Ag(pyrm)CH3COO] respectively as shown in Table 2. The MIC of the silver complexes as presented in Table 3 shows that [Ag2(pyrm)2Cl]_3H2O has an MIC value of 0.03125 mg/mL against all the organisms except for *P. vulgaris* with a value of 0.0625 mg/ml. And for the complex [Ag(pyrm)CH3COO], the MIC value against all the organism is 0.0625 mg/ml. This results indicated that [Ag(pyrm)2Cl]_3H2O has stronger activity. The MBC (minimum bacteria concentration) value which is the lowest concentration of the metal complex that will prevent the bacteria growth was performed. [Ag(pyrm)2Cl]_3H2O has MBC value of 0.03125 mg/mL against all bacteria isolate except *Enterobacter cloacae* and *P. vulgaris* with 0.0625 mg/mL MBC value. [Ag(pyrm)CH3COO] has MBC value of 0.0625 mg/mL against all

the bacteria isolates as shown in Table 3. This result along with MIC results further reveals that [Ag(pyrm)2Cl]_3H2O has a stronger antimicrobial activity. (Idemudia and Ajibade, 2010)

Table 2. Sensitive patters of zones of inhibition exhibited by complexes on some pathogens. (Idemudia and Ajibade, 2010)

Microorganism	$[Ag_2(pyrm)_2Cl]\cdot 3H_2O$ mg/ml	$[Ag(pyrm)CH_3COO]$ mg/ml
Staphylococcus aureus	20.5	22.0
Streptococcus faecalis	18.5	21.5
Bacillus cereus	10.5	15.5
Bacillus pumilus	9.5	16.5
Escherichia coli	9.0	14.0
Pseudomonas aeruginosa	8.0	18.5
Enterobacter cloacae	15.5	19.5
Proteus vulgaris	7.5	12.5

Table 3. The minimum inhibitory concentrations (MIC) exhibited by the complexes against the bacteria isolates. (Idemudia and Ajibade, 2010)

Microorganism	$[Ag_2(pyrm)_2Cl]\cdot 3H_2O$ mg/ml	$[Ag(pyrm)CH_3COO]$ mg/ml
Staphylococcus aureus	0.03125	0.0625
Streptococcus faecalis	0.03125	0.0625
Bacillus cereus	0.03125	0.0625
Bacillus pumilus	0.03125	0.0625
Escherichia coli	0.03125	0.0625
Pseudomonas aeruginosa	0.03125	0.0625
Enterobacter cloacae	0.03125	0.0625
Proteus vulgaris	0.0625	0.0625

Antibiotic activity of cefotaxime metal complexes

Cefotaxime (Hcefotax) interacts with transition metal ions to give [M(cefotax)Cl] complexes (M = Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Cd(II)) which were characterized by physicochemical and spectroscopic methods and a tetrahedral geometry is suggested for their structure. The IR and the ^{1}H-NMR spectra of the complexes suggest that the cefotaxime behaves as monoanionic tridentate ligand . The complexes have been screened for antibacterial activity against several bacteria, and the results are compared with the activity of cefotaxime. (Anacona and Silva2005). The antibiotic cefotaxime belongs to the third generation cephalosporins and resistance to it may be related to the inability of the antibiotic to reach its sites of action, to alterations in the penicillin-binding proteins that are targets of the cephalosporins, or to bacterial enzymes (beta-lactamases) that can inactivate the cephalosporin. The cephalosporins however, have variable susceptibility to beta-lactamase. For example, third generation cephalosporins are more resistant to hydrolysis by the beta-lactamases produced by gram-negative bacteria than first generation cephalosporins. (Anacona and Silva 2005)

Anacona and Silva (2005) reported the synthesis and characterization of cefotaxime metal complexes. The structure of cefotaxime is shown in **Figure 3**

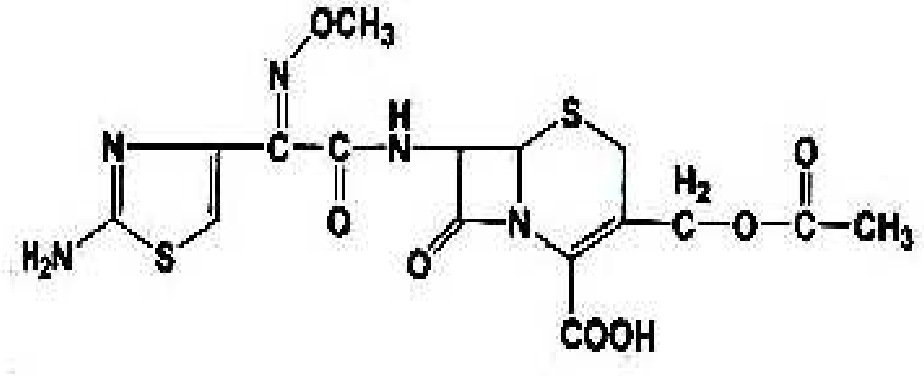

Fig 3. The structure of cefotaxime (Anacona and Silva 2005)

The new suggested structure of cefotaxime

In their own case, Anacona and Silva (2005) reported that the cefotaximate ion has several potential donor atoms but, due to steric constraints, the ligand can provide a maximum of three donor atoms to any one metal center. The assumption that the coordination of cefotaxime occurs through the carboxylate and lactamic carbonyl oxygen atoms seems likely from molecular models. It is feasible that the metal ions in the [M(cefotax)Cl] complexes (where M = Mn(II), Co(II), Ni(II), Cu(II), Cd(II)) are tetra coordinate with one molecule of cefotaxime and the chloride anion at the vertices of a tetrahedron, although octahedral geometries cannot be discarded. On the other hand, the iron(III) complex containing two chloride anions inside the coordination sphere is penta coordinate having probably a tetragonal pyramidal or trigonal bipyramidal geometriy. However, the presence of binuclear structures cannot be discarded. Despite the crystalline nature of the products none proved suitable for X-ray structure determination. The suggested structure can be seen in **Figure 4**

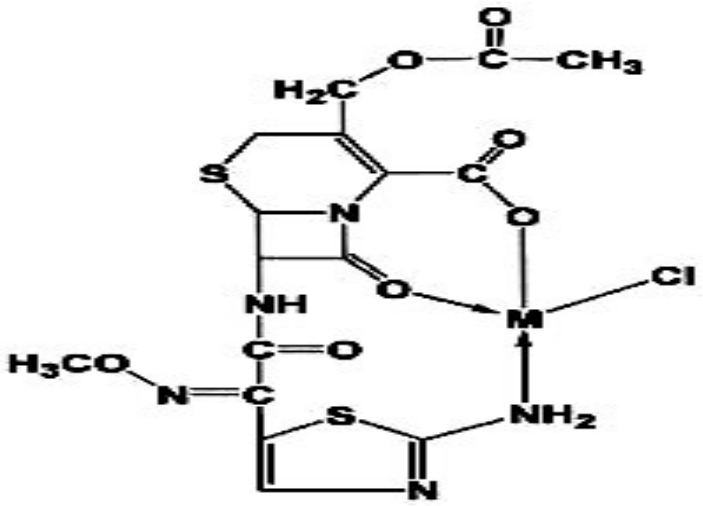

Fig. 4. Tentative structure of the cefotaxime metal complexes [M(cefotax)Cl], (M = Mn(II), Co(II), Ni(II), Cu(II) and Cd(II)). (Anacona and Silva , 2005)

Metal Complexes in Cancer treatment and Research

Previous and recent researches have shown a tremendous success in the use of metal complexes particularly the transition metal complexes in the treatment of cancer.

The therapeutic use of metal complexes in cancer and leukemia are reported from the sixteenth century. In 1960 an inorganic complex cisplatin was discovered, today more than 50 years, it is still one of the world's best selling anticancer drug. Metal complexes formed with other metals like copper, gold, gallium, germanium, tin, ruthenium, iridium was shown significant antitumor activity in animals. (Hariprasath *et al.*, 2010). Transition metals (Ti, V, Cr, Mo, Mn, Fe, Cu and others) have been reported to have antitumour activity, many of which have been modelled on the square planar coordination of cisplatin but a number with octahedral coordination have also been found to be active(Thomas, 2007). Some other transition metals also used as anticancer drugs. Titanium complexes, gold complexes also show significant antitumor activity. In the treatment of ovarian cancer ruthenium compounds containing arylazopyridine ligands show cytotoxic activity. (Loo *et al.*, 2004). At the current time, cis- [Pt(NH3)2Cl2] is one of the most widely used anticancer agents and is the only anticancer agent known that can cure a malignancy. This result has been achieved for testicular cancer when the disease is discovered in its early stages. Because cis-[Pt(NH3)2Cl2] exhibits severe renal toxicity and has narrow applicability to few tumor types, the search has continued for less toxic and wider spectrum platinum-containing anticancer agents. A second drug, [Pt(NH3)2 (CBDCA)] (CBDCA = the cyclobutane-1,1-dicarboxylate ligand), carboplatin has been brought into clinical usage.

Transition metals in Cosmetics

In hair chemistry hair fibres are commonly used as cosmetics. Hair fibres are composed of approximately 85% of the complex protein *keratin,*with some 7% of associated water. The other principal constituents are lipids 3%, and pigment *2%*. This last component is *melanin*, derived in biosynthesis from the amino acid tyrosine. Also present are trace amounts of many metals such as aluminium (Al), calcium (Ca), and many transition metals such as iron (Fe), manganese

(Mn), magnesium (Mg) copper (Cu), chromium (Cr) and zinc (Zn), the last in a fairly high concentration of 22 mg per 100g of hair.(Butler, 2000).

Nickel as one of the transition metals is used in cosmetics as skin sentisizer. To behave as a skin sensitizer a substance must first penetrate the stratum corneum, partition into the epidermis, and react with endogenous proteins to form a hapten–carrier conjugate.

Such substances according to (Leyden and Rawlings,2002)will therefore normally be of low molecular weight (normally<400 D), e.g., metals (nickel).

CONCLUSION

Potential metal-antibiotic drugs and some cosmetics were focused in line with application of biocoordination chemistry which appears to be crucial for improving the design of compounds to reduce toxic side effects and understand their mechanisms of action. This serves as a light cast for chemist interested in developing greener design of drugs and cosmetics.

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