

Current Status on Metal Based Drugs

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Abstract : Now a day's metal based drugs or metallo drugs, have shown promising results in the treatment of various diseases such as diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. in addition to cancer. It was observed that in certain cases the interaction between enzymes and heterocyclic compounds (ligands) was affected by the presence of certain trace amount of metal ion, since metal ions are required in trace amount to form complexes between the ligand molecule and enzymes. Formation of metal complexes results into wide variety of coordination spheres, oxidation states and redox potential, will alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Thus, metal complexes are responsible for drastic change in the biological properties of ligands. Metal complexes exert their biological effect by inhibition of enzymes, interaction with intracellular biomolecules, enhanced lipophilicity and alteration of cell membrane functions etc. Therefore, the present review describes the importance of some metal ions and metal based drugs having promising results in the treatment of various diseases and are being developed as therapeutic agents during the recent past few years.

Introduction

Metals and metal complexes have played key role in the structure and functions of all life forms present on Earth. It can be in the form of metal ions (such as K^+ , Fe^{+2} and Fe^{+3}), composite ions (e.g. molybdate), coordination compounds (like *cis*-platin and carbonyltechnetium), or inorganic molecules such as CO, NO, O₃.

Metal ions play important role in biological processes in the human body for example, Zn (II) and Cu (II) ions are the second and third most abundant transition metals in humans. They are found either at the active sites or as structural components in most of enzymes. Cobalt is present in vitamin B₁₂, a co-enzyme

that plays significant roles in many biochemical processes^{1, 2}. Some of the transition metal ions are effective

therapeutic agents especially when coordinated to a ligand to form metal complexes. In addition to that metal such as platinum, silver, gold, bismuth, antimony, vanadium, iron^{2, 3} are used in chemotherapy for treatment of diseases such as anticancer, antimicrobial, antiarthritic, antiulcer, antiprotozoal, antidiabetic and antimalaria respectively. Besides this, other metal ions like Fe, Mg and Co have diverse role in various biological system such as; magnesium porphyrin complex of chlorophyll is used in green plants for photosynthesis, - cobalt in the co-enzyme B₁₂ for the transfer of alkyl groups

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from one molecule to another molecule.

The amount of metal ions present in the human body is around 0.03% of the body weight. Low or high metal ion concentrations may be harmful for the human.

Heterocyclic molecules (ligands) having electron donor atoms like N, O, S, and P etc. may form coordination bond with various metal ions. Formation of chelation causes drastic changes in the biological properties of ligands and metal ion. In many cases it causes additive effect of both metal ion and ligand⁴⁻⁶. Various mechanisms have been reported for their biological action including inhibition of enzymes, interaction with intracellular biomolecules, enhanced lipophilicity, alteration of cell membrane functions and arrest of cell cycle etc.

Thus, the study of metal-based drugs is broadening rapidly, and a variety of different and distinctive metal based drugs are reported so far, as mentioned below :

(i) Metal compounds as anti-cancer agents:

Platinum drugs : *cisplatin* contains a square-planar geometry in which platinum (II) is a central metal, coordinated to two ammonia ligands and two chloride ligands with a *cis*-conformation.

- iron porphyrin complex of hemoglobin is used in red blood cells (RBCs) for oxygen transportation and storage of oxygen,

Mode of action : *cisplatin* acts through its interaction with DNA. The compound (*cisplatin*) is administered by injection into the bloodstream and is believed to remain in its neutral state until after it crosses the cell membrane where the chloride ligands are displaced by aqua ligands affording cationic compounds. These cationic aqua derivatives react with the bases on DNA, most commonly with the N7 of purine bases, which displace the aqua/chlorido ligands. A bifunctional adduct is formed between the *cisplatin* unit and two adjacent bases on the same strand. Other platinum drugs approved for worldwide clinical uses are : *carboplatin*, *oxaliplatin*, *nedaplatin*, *heptaplatin* and *lobaplatin*. Some of are under commercial development like *satraplatin*, *picoplatin* *miriplatin* and *aroplatin*. Some of the *Trans* and polynuclear platinum drugs have also shown some anticancer activity⁷: These classes of drugs show potencies similar to that of *cisplatin* and, perhaps more importantly, are active against *cisplatin*-resistant cell lines.

In addition to platinum, other metal ions used are Ruthenium, Titanium and gallium for the formation of metal based drugs.

(ii) Metal compounds as anti-diabetic agents:

Vanadium complexes such as bis(α -furancarboxylato) oxovanadium(IV), bis(pyridine-2-carboxylato), oxovanadium (IV) [VO(pic)₂], bis(α -furancarboxylato) oxovanadium(IV), Vanadyl complexes with maltol (3-

hydroxy-2-methyl-4-pyrone) and kojic acid (3-hydroxy-2-hydroxymethyl-4-pyrone) etc. possess insulin mimetic activity and low toxicity profile, have been proposed for clinical use in humans^{6, 8, 9}.

(iii) Metal compounds as antibiotics :

Most of antibiotics do not need metal ions for their biological activities, however, some of the antibiotics such as bleomycin, streptomycin and bacitracin that require metal ions to function properly. The coordinated metal ion in these antibiotics play an important role in maintaining proper structure and functions of such antibiotics. Removal of the metal ions from these antibiotics can cause changes in structure and function of these antibiotics. Metalloantibiotics can interact with different kinds of biomolecules including DNA, RNA, proteins, receptors and lipids rendering them unique and specific bioactivities¹⁰.

(iv) Metal compounds as anti-HIV agents :

Vanadium complexes are well documented to have therapeutic applications. Recent studies showed that oxovanadium (V_2O_3) complexes of thiourea and vanadium substituted polyoxotungstates exhibit potent anti-HIV properties towards infected immortalized T-cells^{11, 12}.

(v) Metal compounds as anti-inflammatory agents :

A large number of transition metal complexes of tolmetin, naproxen, ibuprofen, flufenamic acid, indomethacin, diclofenac, aspirin, piroxicam etc. have been reported as anti-inflammatory agents. Vanadium complexes with the NSAIDs - tolmetin, ibuprofen, naproxen and aspirin have been recently prepared and evaluated for anti-inflammatory activity. Some vanadyl complexes of anti-

inflammatory drugs containing carboxylate ligands have shown promising results¹³. The complexes such as Gold(I) thiomalate [myocrisin (Autm)n], gold(I) thioglucose [solganol (Autg)n] and auranofin [2,3,4,6-tetra-*o*-acetyl-1-thio- β -D-glucopyranosato-(S)-triethylphosphine gold(I)] have been successfully used over many years for the treatment of rheumatoid arthritis¹⁴⁻¹⁶.

(vi) Metal compounds as antimanic agent :

Lithium salts have proved clinical effectiveness for alcohol abuse and aggression, epilepsy, tardive dyskinesia, schizophrenia, Huntington's chorea, premenstrual syndrome, migraine and cluster headaches. Lithium carbonate may be used as in psychiatric disorders such as pathological aggression and reduction in acute or attempted suicide is also recognized^{17, 18}.

(vii) Metal compounds as antimicrobial agents :

Silver and silver containing compounds such as $[Ag(hino)]_2$ (where hino = 4-isopropyltopolone) and silver(I) complexes of (R)-(+)- and (S)-(-)-2-pyrrolidone-2-carboxylic acid, Silver sulfadiazine etc. are used as antimicrobial agents^{19, 20}.

(viii) Metal compounds as antiparasitic agents :

Metal complexes of gold, platinum, iridium, palladium, rhodium and Osmium have been reported to have activity against a variety of trypanosomatids. Chloroquine complex of transition metal ruthenium, $[RuCl_2(CQ)]_2$ has been found to be 2 to 5 times more active than chloroquine diphosphate in *in-vitro* without any acute toxicity²¹.

(ix) Metal compounds as antiulcer agents :

Bismuth compounds such as colloidal bismuth subcitrate, bismuth subsalicylate and ranitidine bismuth citrate are the most widely used drugs for the treatment of variety of gastrointestinal disorders such as diarrhea, dyspepsia and peptic ulcers because of their antacid and astringent properties²².

(x) Metal compounds as antihypertensive agents :

NO compound have varied biological role in human physiology has facilitated the development of NO containing metallopharmaceuticals. They have role in human physiological processes like neurotransmission, blood pressure regulation and immunological responses. Sodium salt of nitric oxide [$\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}]\cdot 2\text{H}_2\text{O}$] is used for the treatment of hypertensive patients. Ruthenium complex of nitric oxide [*trans*- $[\text{Ru}(\text{NH}_3)_4\text{P}(\text{OEt})_3(\text{NO})](\text{PF}_6)_3$] has shown similar antihypertensive activity but reduced toxicity with compared to sodium nitroprusside²³. The peroxy nitrite plays a role in many other pathological conditions such as sepsis, arthritis, diabetes and epilepsy. Ruthenium polyamino carboxylate complexes are efficient NO scavenger²⁴⁻²⁶ and demonstrating their therapeutic potential.

Conclusion

Thus, the role played by metal complexes as therapeutic agents is becoming important in the field of medicinal chemistry. A large number of metal complexes are formed by the use of different metal ions and organic ligand of interest. Metal complexes like cisplatin has proven to be highly effective chemotherapeutic agents for treating various types of cancers.

The use of transition metal complexes offers 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. Besides their certain limitations and side effects, metal complexes are the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics.

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