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– A REVIEW

METALS IN MEDICINE: AN OVERVIEW

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ABSTRACT

Metal ions play many critical functions in humans. Deficiency of some metal ions can lead to disease like pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to understand at the molecular level and to treat diseases caused by inadequate metal-ion function constitutes an important aspect of medicinal bioinorganic chemistry. Metal ions are required in biology for their role as pharmaceuticals as well as diagnostic agents. This review is aimed to provide a historical perspective of the varied roles of various metal ions.

Key words: Metals, Medicine.

INTRODUCTION

Metal ions have been known since long to play vital roles in various cellular processes and their application in therapy has been practiced since ancient Mesopotamian, Indian, Chinese and Egyptian civilizations[1-3]. The field of medicinal inorganic chemistry thus dates back to 3000 BC. However, the introduction of metal binding moiety in biological systems for therapeutic or diagnostic purpose is a rather developing field in bioinorganic chemistry. The metal ion incorporation has significant advantages over conventional diagnostic and therapeutic agents.[4] The contrast agents containing radioisotopes of metals have been effectively used by doctors around the world for single photon emission computed tomography (SPECT)[5,6]. The *in vivo* observation of brain activity, detection of cardiologic problems, malignant lesions and atherosclerosis have all been possible because of the application of contrast agents, especially magnetic resonance imaging (MRI) using Gd^{3+}.[7-10] One of the first examples documented for the use of metals in medicine is salvarsan, arsenic based antimicrobial agent developed by Paul Ehrlich in 1912 for curing syphilis[11]. The exact composition of the drug has eluded scientists for decades and until the World War II, it was used as a standard remedy for syphilis before being replaced by penicillin. However, the serendipitous discovery of cisplatin as a chemotherapeutic agent by Rosenberg in 1965 led to the deluge in the field of metals in medicinal chemistry[12]. Subsequent FDA approval of cisplatin, cis-diamminedichloroplatinum(II), in 1978 had a far reaching impact on the field of chemotherapy, substantially increasing survival for many cancer patients[13-15]. Apart from its clinical value, cisplatin, one of the few approved transition metal based

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drugs, inspired the inorganic chemists to develop their research in medical sciences. This review article aims to highlight role of the myriad of metal based diagnostic and therapeutic molecules.

Metals as diagnostic agents

Diagnostic radiopharmaceuticals are powerful tools in the diagnosis of malignant conditions, cardiologic disorders, kidney infections, liver problems, and neurological disorders[16]. The use of metal based diagnostic agents has significant advantages over the conventional agents used till date. The quality of imaging has improved over the decades and it is now possible to visually detect carcinogenic tissue and differentiate it from healthy ones based on the visual imaging impression before an actual tissue sample is taken. Technetium-99m (^{99m}Tc) is the most popular choice among the diagnostic tracers. This is because it readily emits gamma rays (140 keV) similar to that of conventional X-rays and its suitable half life that allows easy data collections while keeping the patient away from prolonged exposure strong radiation[17,18]. Thus, it is suitable for diagnostic purposes only and not therapeutic functions. ^{99m}Tc imaging agents have been approved over the years by the FDA alone and currently a total of more than 25 ^{99m}Tc imaging agents have been approved by the Food and Drug Administration. However, the major challenge in the use of this versatile isotope lies in the shortage in its production. ^{67}Ga and ^{68}Ga isotopes offer the major advantage of ease of production and hence, are also used for SPECT and PET imaging[19]. Metal chelating agents such as diethylenetriaminepentaacetic acid [H_5DTPA] and 1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7, 10-tetracetic acid [H_4DOTA] on forming complex to the paramagnetic $4f^7$ Gd^{3+} ion are used as macrocyclic contrast agents for MRI scans that can be easily injected into the patients' body[20]. Some of the common metal based diagnostic agents are enlisted in Table 1.

Table 1: Selected metal based diagnostic agents approved by the FDA

Radioisotope	Radiation	Active ingredient	Trade name	Diagnostic imaging
^{67}Ga	γ	Ga-67 citrate		Hodgkin's disease, lymphoma, bronchogenic carcinoma
^{82}Rb	β^+	Rb-82 chloride	Cardiogen 82	Myocardium
^{99m}Tc	γ	Tc-99m bicisate	Neurolite	Stroke
^{99m}Tc	γ	Tc-99m disofenin	Hepatolite	Cholecystitis
^{99m}Tc	γ	Tc-99m mebrofenin	Choletec	Hepatobiliary system
^{99m}Tc	γ	Tc-99m medronate	MDP-Bracco	Bone
^{99m}Tc	γ	Tc-99m pentetate	Technescan HDP	Brain, kidney
^{99m}Tc	γ	Tc-99m sestamibi	Cardiolite	Myocardium, breast
^{99m}Tc	γ	Tc-99m succimer		Kidney
^{99m}Tc	γ	Tc-99m sulphur colloid		Lymphatic system, liver
^{99m}Tc	γ	Tc-99m tetrofosmin	Myoview	Myocardium
^{111}In	γ	In-111 chloride	Indiclor	Radiolabeling of Prosta Scint
^{111}In	γ	In-111		Leukocytes, inflammation

		oxyquinoline	
^{201}T1	γ	Tl-201 chloride	Myocardium, thyroid

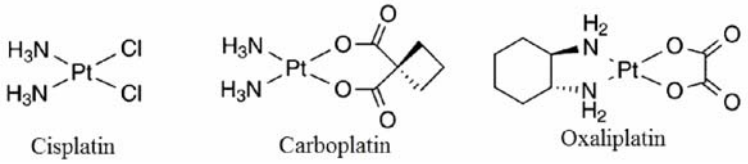
Metals as therapeutic agents

The application of metals for therapeutic purposes ranges from anticancer, antimicrobial, antidiabetic and antiviral agents to those used for the treatment of deficiency diseases, cardiologic conditions and gastrointestinal disorders.

Anticancer agents

Cis-diamminedichloroplatinum (cisplatin) is one of the most renowned anticancer agents known to mankind[13-15]. It is a square planar platinum complex with the metal in the +2 oxidation state. It was first synthesized in 1844 by Peyrone and its anticancer activities were discovered serendipitously by Rosenberg in 1965 while he was studying the effect of electric current on *Escherichia coli* using platinum electrodes. It was found that the process of cell division was inhibited by the production of cis-diammine-dichloroplatinum(II) from the platinum electrodes. The Pt^{2+} of the $[Pt(NH_3)_2]^{2+}$ unit binds covalently to the N-7 of either guanine (G) or adenine (A) in the dinucleotide sequences GG and AG of the DNA to form interstrand crosslink and 1,2 or 1,3 intrastrand crosslinks[21]. The formation of such cisplatin-DNA adducts lead to replication arrest, transcription inhibition, cell cycle arrests, and eventually cell death by apoptosis. To attenuate the side effects of cisplatin, second generation platinum based anticancer agents like carboplatin (cis-diamminedicyclobutane-1,1-dicarboxylato-platinum(II)) and oxaliplatin ((1R, 2R)-(N,N-1,2-diamminocyclohexane)-(O-O)-ethanedioato) platinum (II)) were subsequently developed. The chelate effect of the six member ring in carboplatin is thought to reduce the chemical reactivity of the platinum drug; thus, lowering its nephrotoxicity and ototoxicity. Other drugs in clinical trials in U.S. of similar make include nedaplatin, lobaplatin, and heptaplatin (Fig. 1). Lipoplatin is another such example of lipid encapsulated cisplatin and oxaliplatin that attenuates cytotoxicity is also under clinical trials[22]. Of the platinum drugs in clinical trials, satraplatin (bis(acetato)-amminedichloro (cyclohexylamine) platinum (IV)) offers the unique advantage of oral administration to the patient, which is not only convenient but also cheap. Satraplatin contains a Pt(IV) centre that after administration is reduced to Pt(II), the active form in the bloodstream by the action of redox proteins[23]. A trinuclear platinum complex, triplatin tetranitate was also developed and tested against various forms of cancer. However, severe side effects including nausea and diarrhea stopped it from entering phase III clinical trials[24]. It has been shown that the platinum drugs lose their potency after the initial success because of the intrinsic resistance acquired by the malignant tissues. In this regard, scientists have tried using adjuvant therapy or cocktail therapy using two drugs at a time that operate by different mechanisms[25].

Clinically Approved Platinum Drugs



Platinum Drugs in Clinical Trials (U.S.A.)

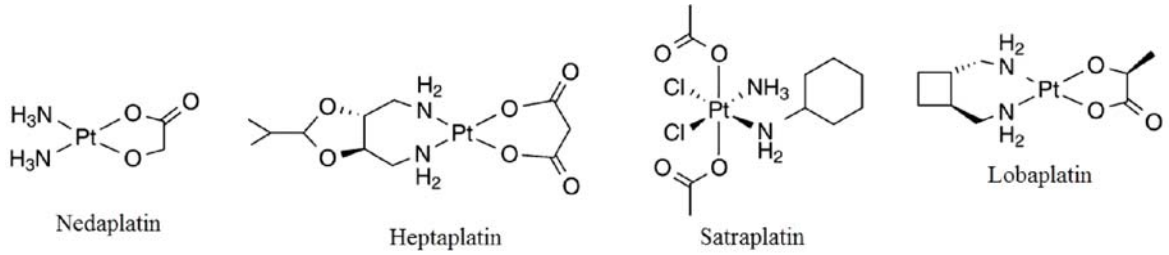


Fig. 1: Examples of the platinum drugs that are clinically approved or undergoing clinical trials

Along with the extensive ongoing research for the development and modification of suitable platinum drugs, ruthenium compounds have also shown promising results as anticancer agents[26]. Ruthenium can be stabilized in different oxidation states and the energy of switching from one to the other is facile under physiological conditions. The complexes are octahedral that further allows better ligand tuning to alter the steric and electronic properties of the complexes. The rate of ligand exchange in ruthenium complexes is slow, which keeps the complexes stable till they reach the target of operation. An advantage of ruthenium drugs is that they are active against metastatic cancers and they are activated by the reduction of the Ru(III) core and transported by transferrin pathway[27]. Dwyer started his work with ruthenium agents as early as in the 1950s. NAMI-A, imidazolium trans-tetrachloro-(dimethylsulfoxide)imidazole-ruthenate (III) was developed by Alessio, Mestroni and others, which was the first ruthenium complex to enter into clinical trials. Keppler's group developed a ruthenium compound, KP1019, trans-tetrachlorobis-(1H-indazole) ruthenate(III) that is also in clinical trials (Fig. 2)[28].

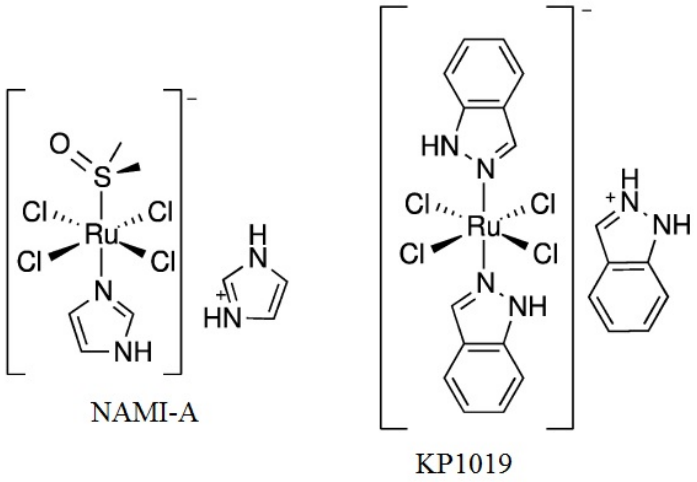
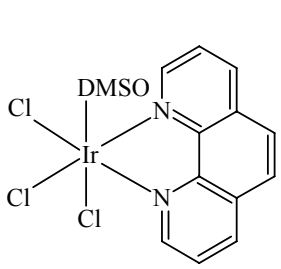


Fig. 2: Examples of ruthenium based anticancer agents that are currently in clinical trials

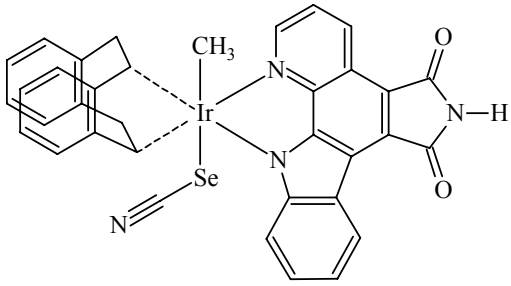
Gallium complexes have also created a niche for them as antineoplastic agents against a broad spectrum of cancers.[29] Gallium nitrate inhibits the proliferation of tumor cells *in vitro* and *in vivo* and has shown activity against non-Hodgkin's lymphoma and bladder cancer in clinical trials. Gallium that can function as an iron mimetic disturbs the iron dependent cell proliferation and other related processes in tumor cells. Gallium nitrate is not myelosuppressive and does not have cross resistance with other chemotherapeutic drugs. Thus, it can be used, when other drugs have failed or when the blood count is low. Given the therapeutic potential of gallium, newer generations of gallium compounds are now in various phases of preclinical and clinical development. Tris(8-hydroxyquinolinato)gallium(III) or commercially

known as KP46 is a chelating agent that has promising anticancer properties and is in phase I clinical trials[30].

Research on iridium complexes as anticancer agents is still in its infancy. Iridium complexes are considered one of the most inert classes of metal complexes. However, this feature is essential for the molecules to reach their target sites without any chemical alterations in their structures. Half sandwich organoiridium complexes with cyclopentadiene and other nitrogen/ oxygen/ carbon donor bidentate ligands have potential anticancer properties[31]. However, the compound trans-[$IrCl_4$(DMSO)(Im)][ImH] (DMSO is dimethyl sulfoxide, ImH is imidazole), the iridium analogue of NAMI-A28 (Ru antitumor metastasis inhibitor on clinical trials), is inert toward hydrolysis and lacks biological activity. Sadler's group has reported several half sandwich iridium complexes, which were found to undergo rapid hydrolysis and were in fact quiet labile.[32] Polypyridyliridium(III) complexes with the general formula fac-[$IrCl_3$(DMSO)(pp)], where pp is bpy, phen, dpq, dppa, or dppn have been reported to have low micromolar activity against MCF-7 breast cancer and HT-29 colon carcinoma cells.[33] Another complex containing N,N-bidentate 5,6-dimethylphenanthroline ligand has been shown to cause concentration dependent apoptosis in Jurkat leukemia cells accompanied by increasing levels of reactive oxygen species. Inert iridium(III) complexes, such as [Ir(DBCOT)(octasporine)(SeCN)(Me)] where DBCOT is dibenzo[a,e]cyclooctatetraene (Fig. 3), selectively inhibit the protein kinase FLT4, as a result of its rigid scaffold. The metal center in this complex plays a dual role: it holds the structural scaffold for molecular recognition of the ATP binding site by the kinase, and allows light induced ligand exchange reactions causing apoptosis in cancer cells.



fac-[$IrCl_3$(DMSO)(bpy)]



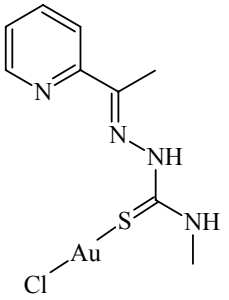
[Ir(DBCOT)(octasporine)(SeCN)(Me)]

Fig. 3: Potential organometallic iridium complexes having anticancer activities

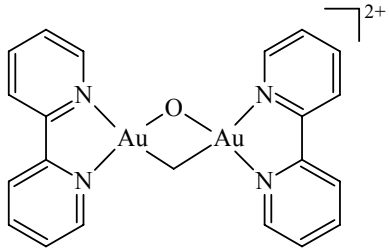
Gold compounds have often been implicated for the inhibition of the TrxR enzyme. Gold(I) can bind strongly to thiolates and selenates that are soft ligands via ligand-exchange reactions. TrxR inhibition by such gold complexes can perturb the mitochondrial function; elevate ROS levels, which may decrease the mitochondrial membrane potential. Thiosemicarbazone derivatives of gold(I), like [Au(H_2Ac_4Me)Cl] where H_2Ac_4Me is N-(4)-methyl-2-acetylpyridine thiosemicarbazone (Fig. 4), inhibit TrxR at micromolar concentrations and are active in acute myeloid leukemia HL60.[34] The selenoenzyme TrxR is also inhibited by gold(I) phosphines such as [AuX(PEt_3)], where X is Cl, Br, CN, or SCN, which exhibit sub-micromolar activities against lung (A549) and breast (MCF-7) cancers, as well as leukemia (HL60). Gold(III) complexes are isoelectronic and isostructural (square planar) with platinum(II) and so have attracted interest as potential anticancer agents. However, rather rigid chelation is required to achieve stability, and the active gold(III) complexes that have emerged appear to act *via* a mechanism different from that of cisplatin. The gold(III) dithiocarbamato complexes reported by the Fregona group generate ROS especially H_2O_2 which impair mitochondrial function.[35] The dinuclear oxo-bridged gold(III) complexes $[Au_2(2,2\text{-bipy})_2(\mu\text{-O})]^{2+}$ (AUOXO1; Fig. 4) and AUXO5 developed in the Messori group are active toward A2780 ovarian cells, and

they retain activity in the platin resistant A2780cis cell line[36]. Here, the mechanism of action is thought to be related to protein interaction because their direct inhibition of TrxR activates the release of cytochrome c.

Arsenic trioxide, popularly known as Trisenox, is used clinically for acute promyelocytic leukemia (APL) since its FDA approval in 2000. Exposure to arsenic alters the natural redox balance in cells because it is capable of reducing GSH levels. Elevation in ROS levels have been related to both the anticancer and mutagenic properties of arsenic derivatives[37,38]. The down regulation of Bcl-2, is thought to be the primary pathway of action of arsenic trioxide, leading to apoptosis. In mitochondria, As_2O_3 inhibits glutathione peroxidase that produces higher levels of H_2O_2 and subsequent changes in the membrane potential. These events result in release of cytochrome c into the cytosol and the activation of programmed cell death *via* caspase-dependent pathways[39].



[Au(n-4-methyl-2-acetylpyridine) Cl]



AUOXO1

Fig. 4: Chemical structures of some gold based complexes with potential anticancer properties

Antimicrobial and antiparasitic agents

Some of the earliest antimicrobial and antiparasitic agents reported were arsenic compounds. Ehrlich and co-workers began their work on arsenic antimicrobials, leading to the discovery of salvarsan as discussed earlier[40]. Although arsenic based pharmaceuticals were developed and used in medicine in the beginning of the 20th century, most of them have been replaced by less toxic drugs. Among the arsenic drug that is still used against trypanosomiasis today, despite its severe side effect of encephalopathy, is melarsoprol, 2-(4-amino)-(4,6-diamino- 1,3,5-triazin-2-yl)-phenyl-1,2,3-dithiarsolan-4-methanol (Arsobal), discovered in 1949. Other pnictogens to be used as antimicrobial and antiparasitic agents include antimony and bismuth compounds. Antimony containing drugs have been prescribed against cutaneous and mucocutaneous leishmaniasis ever since the parasitic transmission of the tropical disease was understood in the beginning of the 20th century. The activity of arsenic against visceral leishmanisis was confirmed, which led to the synthesis of an array of arsenic containing parasitic agents. Among them the less toxic pentavalent antimonials include Stibosan, Neostibosan, and Ureastibamine[41]. Other antimony(IV) drugs like sodium stibogluconate (Pentostam) and melglumine antimoniate (Glucantim or Glucantime) continue to be in use today despite their toxic side effects and increasing loss in potency due to the growing resistance of the parasite against antimony[42,43]. On the other hand, bismuth compounds are reported to be less toxic and the tolerance level is also higher. Since the 18th century, bismuth has been used internally as its subnitrate or subcitrate. Bismuth is known for its action against the bacterium *Helicobacter pylori* that lead to gastritis, ulcers in the gastrointestinal tract and gastric cancer. Bismuth subcitrate or ranitidine bismuth citrate has been used to treat peptic ulcers that are often associated with H. pylori. Moreover, tribromophenatebismuth(III) or popularly known as xeroform was first used for therapeutic purpose because of its antimicrobial properties. Bismuth thiol compounds have also been widely developed and explored for their antimicrobial properties for treating chronic wounds, such as diabetic foot ulcers.

Another metal that has been widely used in the treatment of wounds and treating infection is silver[44]. Topical sulphonamide ointments such as silver sulphadiazine (Silvadene) is used as a cream or aqueous solution (1% silver salt) to prevent and treat burns and infections. Since 1976, cerium nitrate-silver sulphadiazine (Flammacerium) has been used to treat cutaneous burns as it reduces the inflammatory response to burn injury, decrease bacterial colonization, and provide a firm scab[45,46]. Some of the silver drugs are currently in clinical trials. Silver fluoride is used to treat hypersensitivity in teeth while silver nitrate is effective in the healing of cysts. Silver ions are incorporated into surgical wound dressing cloths (e.g., Acticoat) and catheters (e.g., SilverSoaker) for infection prevention or into textiles for the treatment of acute neurodermitis.

A couple of potential metallodrugs that are currently undergoing phase II clinical trials are the antimalaria agent ferrochloroquine (ferroquine, SSR97193, Fig. 5) and the antifungal agent VT1161. Combining ferrocene with the antimalarial drug chloroquine is thought to be a potent agent for overcoming the malaria pathogen *Plasmodium falciparum*. VT1161 is currently in phase 2 clinical trials for the oral treatment of onychomycosis and candidiasis. It is believed to selectively suppress the microbial metalloenzyme lanosterol demethylase (CYP51) involved in the synthesis of fungal cell wall sterols[47].

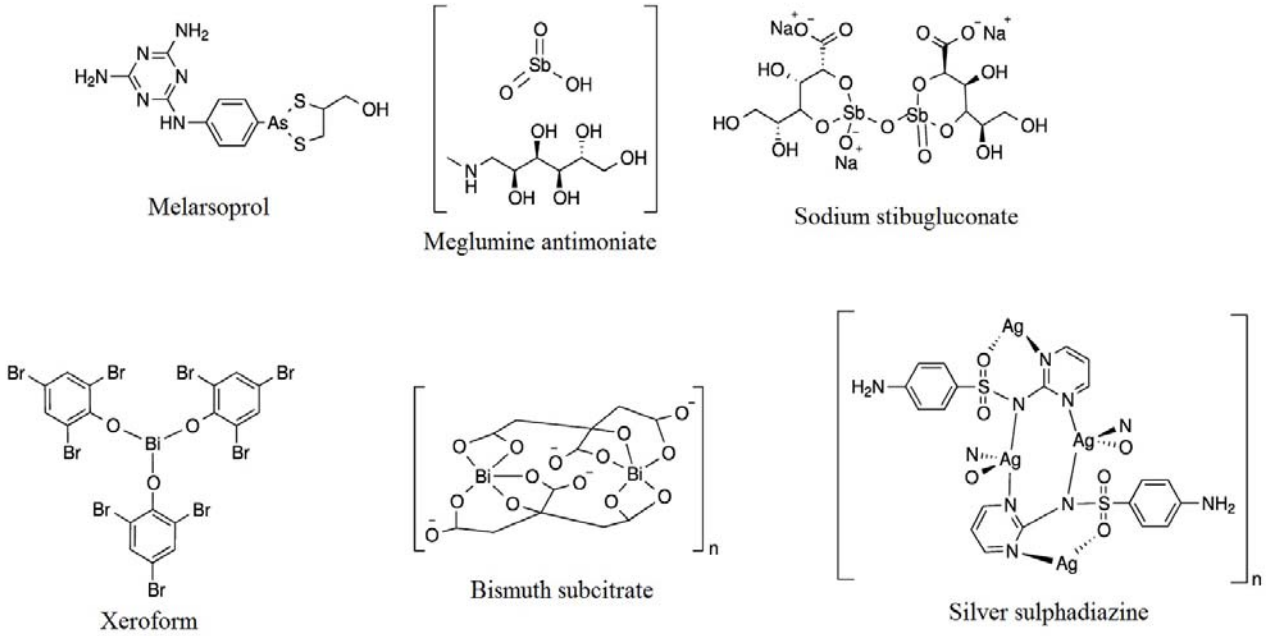


Fig. 5: Examples of various antimicrobial and antiparasitic agents

Antiarthritic metallodrugs

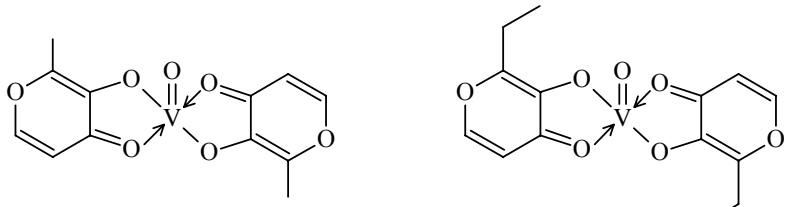
More than 2% of the global population is affected by the chronic, systemic, inflammatory autoimmune disorder rheumatoid arthritis. Though environment, personal habits and genetics play a major role, joint inflammation is common in most of the cases, which eventually lead to the restriction in movements of the patients. Forestier realized the potential of gold compounds in the treatment of rheumatoid arthritis as early as 1930s.[48] Many of the gold thiosulfates that are still in clinical use today were introduced in the early 20th century. Among them, sodium aurothiomalate (Myochrysine, Myocrisin, Tauredon), aurothioglucose (Aureotan, Solganal, Solganol, Auromyose), sodium aurothiopropanol sulfonate (Allochrysine), and sodium aurothiosulfate (Sanochrysin) are the most commonly available gold based drugs. These are charged polymeric species, which are directly injected to the muscles of the patients' body.

Another drug, auranofin, tetraacetyl-β-D-thioglucose-gold(I)-thioethylphosphine that received FDA approval in 1985, is a monomeric, neutral coordination compound that is lipophilic and administered orally in capsule form. Despite all the clinical success, gold compounds, their efficacy and safety has been scrutinized for decades.

Osmium tetraoxide solutions were used for the treatment of rheumatoid arthritis in the 1950s especially in Scandinavian countries[49,50]. It has been shown to efficiently catalyze the dismutation of superoxide anion radical, one of the primary inflammatory species[51].

Antidiabetic agents

It has been estimated that globally 347 million people have diabetes mellitus (DM), and the numbers are increasing[52]. Vanadium salts and other coordination compounds have demonstrated various insulin enhancing and antidiabetic effects[53]. Sodium vanadate was first used by Lyonnet in 1899, which showed positive effect on the health of diabetic patients[54]. The potential of vanadate as phosphatases inhibitory agent was shown by Josephson in 1977.[55] These observations triggered extensive research on the biological functions of vanadium, and vanadium (IV, V) coordination complexes with a variety of organic ligands[56-58]. Bis(maltolato)oxovanadium (IV) (BMOV) and its ethylmaltol analogue bis(ethylmaltolato) oxovanadium (IV) (BEOV), (Fig. 6), exhibited increased *in vivo* bioavailability over vanadyl sulfate[59]. The insulin enhancing effect of such vanadium complexes is thought to stem from the activation of the insulin receptor through the suppression of insulin receptor tyrosine kinase (IRTK) associated phosphatases. Vanadium formulated with Aonys for the treating metabolic disorders has successfully completed phase I clinical trials. The reverse micelle emulsion containing vanadium is applied to the mucous membranes lining the inside of the mouth using a spray pump, which reduces active doses from the mg/Kg to the μg/Kg level. This avoids the side effects associated with high doses of vanadium in the earlier oral formulations[60]. Again sodium tungstate (Na_2WO_4) was reported to reduce glycemia and adiposity in animal models without any significant side effects[61].



BMOV BEOV

Fig. 6: Chemical structures of vanadium based antidiabetic agents

Other applications of metal based therapeutic agents

Deficit of essential metal ions leads to various deficiency syndromes that can often be fatal. Malnutrition can be treated temporarily or over longer time periods using dietary supplements consisting of one or more metal ions. Iron deficiency is the most prevalent and more than 2 billion people are affected by it worldwide. Certain metal deficiencies arise from genetic metabolic disorders (acrodermatitis enteropathica, Menkes disease) while others occur as a consequence of complications in cases of gastric atrophy or chronic kidney disease. Acrodermatitis enteropathica is an autosomalrecessive metabolic disorder affecting the uptake of zinc for which patients depend lifelong on zinc supplements to survive. Similarly Menkes Disease is caused by a mutation on the gene encoding Cu^{2+} transporting ATPase that leads to the dysfunction of many copper dependent enzymes and acute copper deficiency. Immediate treatment can prevent brain damage. Copper histidine complex is in phase II clinical trials for the treatment of MD.

Anemia is yet another prevalent condition especially in developing and under developed countries which occur due to the deficit of Fe^{2+} ions. Iron dextran (Proferdex, Dexferrum, InFeD) or iron sucrose (Venofer) are administered intravenously to treat severe iron deficiency conditions.

Another common problem in cancer patients is hypercalcemia or the imbalance between the net resorption of bone and urinary excretion of calcium. Through infusions of gallium (III) nitrate (Ganite), the calcium resorption from bone is reduced, as gallium (III) exerts a hypocalcemic effect[62]. Osteoporosis is yet another disease characterized by low bone mass and deterioration of bone tissue leading to enhanced bone fragility leading bone fractures[63]. Primarily, such osteoporotic fractures affect the hips and knees of postmenopausal women, but men and children can as well be struck by osteoporosis. Essential micronutrients like calcium, magnesium, phosphorus, fluorine, vitamin D, and proteins are given to patients suffering from osteoporosis. Strontium ranelate is approved for the treatment of osteoporosis in some European countries and Australia but it is being restricted because of its cardiologic implications.

CONCLUSION

The field of metallodrugs in medicinal inorganic chemistry has grown constantly during the past five decades. However, despite the tremendous advancement of a few metallodrugs, the discipline is still in infancy as compared to the traditional medicinal chemistry areas of small organic or biological drug molecules. Several discoveries in science have been made by accident, and the serendipitous discovery of the anticancer activity of platinum or the antiarthritis activity of gold or the antidiabetic activity of vanadium are exemplary cases. To exploit fully the potential of metallodrugs, it is absolutely essential to understand fate of the coordination complex and its components, the metal and the ligand(s), once the metal-ligand complex enters the body. This review has discussed the important FDA approved diagnostic and therapeutic metallodrugs, their limitations and the strategies adopted to overcome them.

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