

Review Article

<https://doi.org/10.20546/ijcmas.2020.902.294>**Dynamics of Transition Metal and their Application in Biomedical Industry**Pijush Malpaharia¹ and S. K. Pandey^{2*}¹Department of Chemistry, ²Department of Botany, Jamtara College Jamtara-815351, S.K.M. University, Dumka, Jharkhand, India**Corresponding author***A B S T R A C T**

The transition metals are a group of metals that are found in the middle of the periodic table. The alkaline earth metals, beginning with beryllium are to the left and the boron group elements are to the right are termed as "transition element". There are more transition metals than any other groups in the periodic table. Transition metals have several general properties. They are harder and less reactive than the alkaline earth metals. They are also harder than the post transition metals. They make colorful chemical compounds with other elements. Most of them have more than one oxidation state. Like other metals, they are electrical conductors. Some of the transition metals are necessary for human health, such as iron, zinc, and chromium. Other elements in the transition metals can be harmful to our body, like cadmium and mercury. Other elements like gold or silver do not harm or help us. Only a few of the transition metals are colored; most of them are silver-gray or silver-bluish. The oxidation activity of transition metals led to the recent development of drugs which are based on metals and are considered to be potential for pharmacological and therapeutic applications. This review emphasizes on preclinical pharmacological screenings like anti-microbial, anti-inflammatory and anti-tumor action of synthetic transition metal complexes. It concentrates primarily on a limited number of first row transition metal complexes and traces the pharmacological applications of these coordination compounds. In the first part, the nitrogen, oxygen and sulfur donor ligands chelating to transition metals used in metallo drugs are described. The second part describes the pre-clinical screenings viz., anti-microbial, anti-inflammatory and anti-tumor responses of the above coordination compounds incorporating these nitrogen, oxygen and sulfur donor ligands. This survey encourages further research in this field for biomedical industry.

Keywords

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Introduction

Transition metals are often highly reactive due to their strong propensity toward oxidation to more stable high-valent states. Harnessing these highly reducing complexes for productive reactivity is potentially

powerful for C–C bond construction, organic reductions, small-molecule activation and many other reactions that offer orthogonal chemo selectivity and region selectivity patterns to processes promoted by late transition metals. Ions of metal play important roles in different biological processes. The field of knowledge related to the application

of inorganic chemistry to diagnosis of diseases and their therapy is medicinal inorganic chemistry [1]. Among the natural sciences, medicinal inorganic chemistry is still considered a rather young discipline which is contrary to the historically proven use of metals in pharmaceutical potions, which traces back to the ancient civilizations of Mesopotamia, Egypt, India, and China [2]. The introduction of metal ions binding components into a biological system for the treatment of diseases is one of the emerging fields of bioinorganic chemistry. A wide range of biological activities such as antibacterial, antifungal, antitumor and antiviral activities are exhibited by the nitrogen-containing organic compounds and their metal complexes. Transition metal complexes offer two distinct advantages as DNA-binding agents which often show distinct electrochemical or photophysical properties, thereby increasing the functions of the binding agent [3]. In fact, these peculiar features have fuelled the complexes to be used in different applications, from fluorescent markers to DNA foot printing agents and electrochemical probes [4].

Among the metal ions platinum and ruthenium ions are commonly explored as coordination centers of potential anticancer agents, [5]. They are most abundantly occurring trace elements present in biological systems together with iron [6]. Less toxic nature of these targeting metal ions can be further decreased when coordinated with the ligands particularly. Though there are so many ligands are available i.e. N-heterocycles (1,10 Phenanthroline, Bipyridine) and pyrazolones with an added benefit to their properties which is a major advantage in designing an ideal drug. Amino acids are the building blocks of our body and when the drug is similar to that of the functions inside the body there is maximum chances of succeeding in designing a less toxic and

efficient cheap drug. In addition to that, the N-heterocycles and pyrazolones as ligands affect the environment of the complex in such a way that their lipophilicity increases which is a leading factor in designing a drug.

The method used for this review is mainly based on secondary data. It follows a descriptive study and focuses on creating a detailed picture by identifying, obtaining, describing and analyzing available documents, published government policies, lectures-statements by government leaders and other views related to the research problem. In order to compile this manuscript the works related to the transition metals used in biomedical industry from the important journals, magazines, survey materials, periodicals, reports, booklets, newspapers, books published in India and abroad were taken into consideration.

Transition metals and biomedical industry

There are a large number of chemicals used in biomedical industry. However, the chemicals which contain transition metals are of high therapeutic and curative value. Some of the common and effective chemicals are depicted below in brief:

Bioactive chelating agents

Aliphatic Schiff bases are relatively unstable and easily polymerizable in comparison to other aromatic Schiff bases [7]. Their derivatives represent one of the modest classes of biologically active agents which have been deeply studied during a search on new potential agents which are widely used for synthesis purpose [8]. These ligands have received much attention mainly due to their antimicrobial, anti-tuberculosis, antitumour activity, anticonvulsant, anti-inflammatory, anti-HIV, anthelmintic and cardiovascular activities and anti-carcinogenic properties [9].

Amino acids

Schiff bases derived from amino acids are found to be very effective metal chelators. Their metal complexes are models for a number of important biological systems [10]. They are the key intermediates in a number of metabolic reactions involving amino acids such as decarboxylation, transamination and racemization which are catalyzed by enzymes [11]. Synthetic ligands with longer chains are preferred for pharmacological purposes are another fact to be considered.

Amino acids can act as coordinating agents through their amino (NH_2) and carboxylate (COO^-) groups [12]. For sulfur-containing amino acids, the SH group confers a more versatile coordination activity toward heavy metal ions. The $-\text{SH}$ (sulfhydryl), $-\text{NH}_2$ (amino) and $-\text{COO}^-$ (carboxylate) groups are the possible coordination sites for the complexation processes. Sequestration of toxic heavy metal ions and obtaining safer drugs or antidotes for metal poisoning [13] by complexation is a very promising field.

The uncontrolled movement of metal ions in the human body leads to the formation of reactive oxygen species such as superoxide anion radical (O_2^-), singlet oxygen ($^1\text{O}^2$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($^{\cdot}\text{OH}$). Thus they can oxidize the biochemical molecules thereby disturbing the homeostasis in an organism.

Recently, Several experiments have evaluated the efficiency of antimicrobial potential of 2-nitrobenzaldehyde–glycine and 2-nitrobenzaldehyde–methionine against the growth of bacteria *in vitro* [14].

Pyrazolones

Pyrazolones are a class of organic compounds which have been studied extensively due to

their biomedical properties [15]. Pyrazolone is a five-membered lactam ring which contains two nitrogens and a ketone in the same molecule and is an active moiety in pharmacological activity such as anti-inflammatory and analgesic agents [16].

It is an active moiety as the pharmaceutical ingredient, especially in non-steroidal anti-inflammatory drugs (NSAID) and is used in the treatment of cancer, arthritis and other musculoskeletal and joint disorders. Scientists have recently synthesized a Schiff base complex of copper with 5-dimethyl-2-phenyl-4-[(pyridin-2-ylmethylene)-amino]-1,2-dihydro-pyrazol-3-one and investigated its DNA binding propensity, nuclease, radical-scavenging and anti-cancer cytotoxic activities [17].

Nitrogen heterocycles

They are one of the most important classes of ligands in coordination chemistry [18,19]. In addition, 1,10-phenanthroline has shown retardation of growth of a Sarcoma-37 tumor [20] and it inhibits the cell proliferation of Ehrlich ascites [21]. This will be more permeable through the cell membrane and eventually behave as carriers of antitumor agents [22, 23].

Bipyridine

2,2'-bipyridine is a chelating component. The 2,2'-bipyridyl moiety has been extensively used as a chelating donor site within such bridging ligands due to its robust redox stability [24]. This allows ligands containing multiple 2,2'-bipyridine units to be synthesized and the interconnection of metal centres to be achieved with well-defined spatial arrangements. This has been directed towards the study of metal–metal interactions in supramolecular chemistry to study anion–interactions as sensors in new coordination

materials and as structural and functional enzyme active site models [25].

Mode of action of transition metal complexes

The application of transition metals and its compounds in medicine dates back to millennia which provide an experimental evidence for the effectiveness of such metal-based therapeutics. The chelates of transition metal play a significant role in bio-inorganic chemistry and redox enzyme systems serve as the basis of models for active sites in biologically important compounds [26]. These metals have different coordination geometry, versatile redox, spectral and magnetic properties which are appropriate for designing non-porphyrinic metal-based PDT agents that could photo cleave DNA in visible light. The relationship between vibrant metals and cancer is a multifaceted issue which combines the expertise of bioinorganic chemists, pathologists, pharmacologists and oncologists. Redox-active metals generally form reactive oxygen species (ROS) and this ROS can be used to induce DNA cleavage. Moreover, it cures only limited spectrum of cancers and acquired resistance [27]. To defeat these limitations of cis-platin, less toxic and more effective metallo drugs like oxaliplatin and carboplatin have been developed. DNA is the storage place of cellular information that is accessed continuously for storing and dispensing information required for existence. It acts as the main intracellular target for those who thrive to develop a new drug for innumerable diseases, particularly cancer. It is significant for the function of several enzymes and proteins involved in energy metabolism, respiration and DNA synthesis, particularly cytochrome oxidase, superoxide dismutase (SOD), ascorbate oxidase and tyrosinase [28]. Copper is found to bind DNA with high affinity than any other divalent cation, thus

promoting DNA oxidation. The copper complexes synthesized by Gup and Gokce are found to bind significantly to calf thymus DNA by both groove binding and intercalation modes and effectively cleave pBR322 DNA. Most common medicinal uses of transition metal complexes are as follows:

Anticancerous agents

Chemotherapy using chemical agents is one of the effective methods for the treatment of various cancers. With the increasing number of compounds synthesized as potential anticancer drugs, effective screening methods are needed for classification of these compounds according to their anticancer activities [29]. The increasing number of multi-drug resistant microbial pathogens hardened the treatment of infectious diseases that posed as an important and challenging problem. Despite the availability of a large number of antibiotics and chemotherapeutics, a substantial need for the development of new class of potent antimicrobial agents arose on account of the emergence of old and new antibiotic resistant bacterial strains. Thus, the heterocyclic compounds play a considerable role in designing a new class of structural entities of medicinal importance with new mechanisms of action [30]. The diverse pharmacological properties possessed by heterocyclic compounds are the well known antimalarial, antimicrobial, anti-inflammatory, anticancer, analgesic and anticonvulsant. The superoxide dismutases (SODs) known as metallo enzymes are able to keep the concentration of superoxide radicals in convenient low limits and thus, they can protect cells against an oxidative damage [31]. Recently it has been found that reactive oxygen species, such as the superoxide radical or hydrogen peroxide are important regulators of apoptosis [32]. Particularly, H_2O_2 is implicated as a mediator of the cell death. The cellular damage caused by H_2O_2 is due to the

hydroxyl radical production that results from the reaction of H₂O₂ with transition metal ions [33].

Anti-microbial agents

The latest review focuses on the crisis of decrease in quinolone drug absorption when consumed simultaneously with magnesium or aluminium antacids. The work was emphasized on crystal structures of quinolone-metal compounds and their anti-microbial activities [34]. The reason for such behaviour is proposed to be the chelate bonding of the quinolone to the metal. The complex [Cu(cx)₂]. 2H₂O (where cx = cinoxacin) was screened for activity against several bacteria [minimal inhibitory concentration (MIC) values] showing the same antimicrobial activity as the free ligand. The complexes were screened for antimicrobial activity against various bacterial and fungal species viz., *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *A. niger* and *C. albicans* by disc diffusion method. The Cu complex exhibited the highest zone of inhibition against the bacterial species viz. *K. pneumoniae* (12 mm) and *P. aeruginosa* (11 mm). The Ni mixed ligand complex exhibited a higher zone of inhibition against *E. coli* (12 mm) and Zn complex exhibited a higher zone of inhibition against *Streptomyces. aureus* (12 mm) [35]. From the above experiments it was concluded that among the four mixed ligand metal complexes, Cu mixed ligand metal complex showed higher antibacterial activity. In the case of antifungal activity, Co complex showed the higher zone of inhibition against the fungal species *C. albicans* (13 mm) and Ni complex showed higher activity against *A. niger* (8 mm). Overall, the antimicrobial activity of the complexes is in the following order: Cu>Co>Ni>Zn. The dominance of the metal complexes may possibly be as a result of increased lipophilic nature of the complexes attributed to chelation and

heteroatoms present in the ligand moiety [36,37,38].

Anti-tumor agents

There are several reports available about the ternary copper complexes, that are synthesized by the combination of a bidentate N-donor heterocyclic ligand (phen, bpy or their substituted derivatives) and other synthetic co-ligands (i.e., salicylic acid, tetracycline derivatives, terpyridine, or imidazolidine-2-thione), with remarkable *in vitro* cytotoxicity towards the human cancer cell lines [39]. However, none of these dealt with the directed synthesis of mixed ligand copper coordination compounds containing flavonoid-inspired co-ligands. Lately, Rajendiran *et al.*, (2007) have found that efficient self-activated DNA cleavage and cytotoxic effects toward L1210 murine leukemia and A2780 human ovarian carcinoma cell lines can be brought out by the complex [Cu (pyrimol) Cl], synthesized by them [40,41]. Harding and his co-worker have synthesized bis (η⁵-(3,4- dimethoxybenzyl) cyclopentadienyl)-vanadium dichloride complex. Further *in vitro* and *in vivo* work revealed that V(IV) organometallic compounds exhibit significant anti-tumor properties with vanadocene dichloride being one of the most promising among metallocenes[42,43]. By comparing the cytotoxicity with that of the conventional standard cisplatin, they found that the complexes exhibited excellent activity in both the cancer cell lines. However, the cytotoxic activity of complexes against human breast cancer cell line stood higher than that of skin carcinoma cell line [44, 45].

Anti-inflammatory agents

The protective response of an organism, when treated by a noxious stimulus is known as inflammation. Such inflammatory conditions lead to rheumatic diseases. It is a part of the

complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells and irritants. Recent experiments revealed that 3,5-diaminodiamido-4-oxahexacyclododecane (cageL) can survive *in vivo* through a demonstration by speciation calculations using blood plasma model and animal bio-distribution experiments, which is due to the stability in lipophilic conditions [46, 47]. In pursuit of developing better copper based anti-inflammatory drugs which can be administered orally, intravenously or even transdermally, they have designed and synthesized two ligands, N, NO-di(aminoethylene)-2,6-pyridinedicarbonylamine (L1) and bis-(N,Ndimethylethyl)-2,6-pyridinedicarboxamide (L2). L1 and L2 both have pyridyl groups which are found in most of the non-steroidal anti-inflammatory drugs (NSAIDs) [48]. A class of quinoline based compounds has been explored and found to have the ability to inhibit platelet-activating factor (PAF) synthesis which also contributes to anti-inflammatory properties [49]. The role of copper in the pathology of inflammation emphasizes a lot of evidence [50]. The thorough investigation of copper complexes with different ligands together with anti-inflammatory drugs and of the copper containing enzyme super oxide dismutase (SOD) brought to light the various therapeutic value of copper which is concluded to be an exogenous anti-inflammatory agent. Scientists have explored a series of Schiff bases derived from 2-mercapto-3-formyl quinoline/2-hydroxy-3-formyl quinoline with 2,6-diaminopyridine (DAP) and their corresponding Co (II), Ni (II), Cu (II) and Zn (II) complexes for their anti-inflammatory activity. The Cu (II) complexes showed the highest biological activities amongst the compounds tested [51].

A series of potential anti-inflammatory agents that are Co (II) complexes and bearing the

NSAID mefenamic acid ligand have also been investigated [52]. Mefenamic acid is found to act as a deprotonated monodentate ligand. It is coordinated to the Co (II) ion through its carboxylato oxygen atom, forming octahedral $[\text{Co}(\text{mef})_2(\text{MeOH})_4]$ or $[\text{Co}(\text{mef})_2(\text{MeOH})_2(\text{N}^{\wedge}\text{N})]$ (where mef = mefenamic acid and $\text{N}^{\wedge}\text{N}$ = 2,2'-bipyridine, 1,10-phenanthroline or (pyridine)₂) complexes which is in accordance with the physicochemical and spectroscopic data. In later studies, Cu(II) complexes of mefenamic acid, naproxen, diclofenac, diflunisal and flufenamic acid, Co (II) complexes of naproxen and tolfenamic acid, and Mn (II) complexes of tolfenamic acid have been reported by the researchers that showed anti-inflammatory activity[53].

Conclusions and future directions as follows:

The application of bioinorganic chemistry to medicine is a rapidly developing field. Novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Advances in bioinorganic chemistry are important for improving the design of compounds to reduce toxic side-effects and understand their mechanisms of action. This review reveals that the pharmacologically interesting metals such as copper, cobalt, nickel and zinc could be a suitable strategy to develop novel therapeutic tools for the biomedical industry.

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