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Metalloantibiotics and antibiotic mimics - an overview

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ABSTRACT

The metal cores of metalloantibiotics offer a unique prospect to probe their structure and function at functional groups that can readily be distinguished from the surrounding environment. Metalloantibiotics interact with DNA, RNA, proteins, receptors and lipids, making them very unique and specific. Metal contamination potentially contributes to the maintenance and spread of antibiotic resistance factors. Certain metal ions binding with antibiotics (bleomycin, histatin, and bacitracin) and the Alzheimer's disease-related β-amyloid peptide exhibited specific biological activities and chemical reactivities. Bismuth-fluoroquinolone complexes have the potential to be developed as drugs against *H. pylori* related ailments. Antibiotics metal complexes as well as mixed antibiotics metal complexes were found more effective as chemotherapy agents than their parent antibiotics. The addition of vitamin C markedly enhanced the activities of both pomegranates/Fe (II) and pomegranates /Cu (II) combinations against *S. aureus*.

Key words: Metalloantibiotics, antibiotics, metal, complexation, antibiotic mimics

1. Introduction

The term antibiotic refers to natural or synthetic/ semisynthetic compounds that in, minute concentrations, inhibit the growth of or kill microorganisms completely[1]. Examples of antibiotics produced and isolated from living organisms include aminoglycosides. The sulfonamides, the quinolones, and the oxazolidinones are examples of purely synthetic antibiotics. Semisynthetic (modified chemically from original compounds found in nature) include beta-lactams (which include the penicillins, produced by fungi in the genus *Penicillium*, the cephalosporins, and the carbapenems). Antibiotics are used to treat bacterial infection in humans and animals.

Metalloantibiotics: Metals have an esteemed place in medicinal chemistry. Although most antibiotics do not need metal ions for their biological activities, there are a number of antibiotics called metalloantibiotics [2] that require metal ions to function properly. This is due to the fact that metal ions can interact with many different kinds of biomolecules, including DNA, RNA, proteins, receptors, and lipids, rendering their unique and specific bioactivities. The metal binding properties, structures, and chemical reactivities of metallopeptides such as the bacterial antibiotic bacitracin, the Alzheimer's disease-related β-amyloid, and the salivary antimicrobial histatin have been reported [3]. The techniques used in metalloantibiotics research include high field multidimensional NMR, chromatography, computer graphics, optical spectroscopy, chemical (and combinatorial) synthesis, X-ray crystallography, and mass spectrometry.

Some metal complexes are known to exhibit remarkable antitumour, antifungal, antiviral and special biological activities and the efficacies of some therapeutic agents are known to increase upon co-ordination[4-9]. Some metal-based antibiotics such as bleomycin, streptonigrin, and bactracin have gained recognition and are more effective than pure drugs [2]. Cobalt complex with histidine ligand showed the significant antibacterial and antifungal activity in comparison with commercial antibiotics [10].

The development of metal-based drugs with promising pharmacological application has been reported as transition metals can interact with a number of negatively charged molecules due to different oxidation states they possess[11]. Researchers have reported the binding of Fe/ Co-bleomycin, Fe/Cu-streptonigrin, Mg-quinolone, Mg-quinobenzoxazine, Mg-aureolic, metal ions-siderophores/ ionophores, metallobacitracin to undecaisoprenyl pyrophosphate which enables the microorganisms. The binding of redox active metal ions to bleomycin and streptonigrin entitles these antibiotics to act as potent DNA cleavaging agents, and the divalent metal complexes of

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bacitracin bind to long-chain isoprenyl pyrophosphates which resulted in the inhibition of cell wall synthesis [2]. Complexation between Cu(II), Mn(II) and some antibiotics has shown that the site of complexation is a function of the side chain and also of pH [12].

The metal cores of metalloantibiotics present a unique opportunity to probe their structure and function at functional groups that can readily be distinguished from the surrounding environment by spectroscopic techniques. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorders[10]. DNA can bind many different biomolecules and synthetic compounds, including polyamines, and synthetic metal complexes and organometallic compounds [13-15].

2. Classes of metalloantibiotics:

There are many different classes of metalloantibiotics, each exerting a different type of inhibitory effect that specifically impacts bacteria.

2.1 Aminoglycosides: Aminoglycosides form a unique and structurally diverse family of antibiotics, which include the famous Waksman's streptomycin and the widely used neomycin (an ingredient in''triple antibiotic''ointment along with bacitracin and polymyxin B). Antibiotic aminoglycosides work by inhibiting protein synthesis in bacteria and compromise the structure of the bacterial cell wall. The mode of action involves binding to the bacterial 30S ribosomal subunit (some work by binding to the 50S subunit) and inhibit the translocation of the peptidyl-tRNA. (e.g. Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin, Paromomycin, Streptomycin). Neomycin has also been determined to inhibit the self-cleavage of the ribozyme from human hepatitis virus by direct replacement of the active divalent metal ions. Aminoglycosides work against infections caused by Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella* specialy *Pseudomonas aeruginosa* and are effective against aerobic bacteria. The ability of aminoglycosides to bind metal ions is primarily governed by sugar ring substitution on the 2-deoxy streptamine ring (Ring B). Vicinal amine and hydroxyl groups can form a potential metal chelating motif, as found within the 2-deoxy streptamine ring (1-amine and 6-hydroxyl) [16]. Gentamicins also possess metal chelate donor atoms in ring C [17,18].

Aminoglycoside phosphotransferase (3')-IIIa (APH) has broadest substrate range among the phosphotransferases that cause resistance to aminoglycoside antibiotics. The presence of metal-nucleotide increased the binding affinity of aminoglycosides to APH. In addition, the replacement of magnesium (II) with manganese (II) lowered the catalytic rates significantly while affecting the substrate selectivity of the enzyme such that the aminoglycosides with 2'-NH(2) become better substrates (higher V_{max}) than those with 2'-OH [19]. Aminoglycosides can be considered as "metal mimics" [20] because they bind to metal-ion binding sites of RNA molecules and interfere with the function of RNA by displacing functionally/structurally important metal II) ions. Aminoglycosides promoted biochemical activities of a large ribozyme by acting as a Mg^{2+} mimic [21]. Scientists showed that aminoglycosides also interfere with metal-ion binding sites of protein enzymes, showing that the "metal mimics" property of aminoglycosides is not only restricted to the interaction between aminoglycosides and RNA[22]. Thus, aminoglycosides as "metal mimics" have the potential to be used as functional probes to perturb the catalytic activity of both ribozymes and metalloenzymes, and, as functional/structural probes, to map and characterize the active sites of such catalytic activities.

2.2 Ansamycins: Ansamycins prevents bacterial cell division by inhibiting cell wall synthesis. 17-(allylamino)-17-demethoxygeldanamycin (17AAG), a benzoquinone ansamycin Hsp90 inhibitor, has promising anticancer activity *in vitro*, in animal models and in clinical trials. It was demonstrated that $17AAGH_2$ was a more potent Hsp90 inhibitor than its parent quinine; however, $17AAGH_2$ can be oxidized back to 17AAG under aerobic conditions. Results suggested that human serum albumin prevented $17AAGH_2$ oxidation via a copper chelation mechanism [23].

2.3 Carbacephems: Carbacephems inhibit cell wall synthesis. Iron-dependent pathogen control is a promising field and offers a broad array of possible therapeutic applications. While the siderophore-antibiotic strategy uses Fe-siderophore uptake systems as gateways for cellular infiltration with established antibiotics, the siderophore pathway inhibition strategy tries to abolish siderophore

utilization in order to starve the pathogens out for iron. Both concepts proved to be successful with *in vitro* and *ex vivo* culture model systems. However, most of these compounds have to be evaluated in appropriate *in vivo* systems. The crystal structure of the Fe-enterobactin binding protein CeuE was found in a status of ligand-dependent dimerization, which was observed upon cocrystallization with the synthetic enterobactin analogue 1,3,5-N,N',N''-tris-(2,3-dihydroxybenzoyl) triaminomethylbenzene (MECAM), possessing an aromatic backbone. The ligand dimerization that led to the face-to-face joining of two periplasmic binding proteins was dependent on the iron bound to the ligand complex and the π-stacking interactions between the aromatic backbones of the ligand molecules [24].

2.4 Carbapenems: They inhibit cell wall synthesis. Metal analyses demonstrated that recombinant metallo-β-lactamase Bla2 from *Bacillus anthracis* tightly binds 1 equiv of Zn(II). Results showed that mono-Zn(II) Bla2 (1Zn-Bla2) was active, while di-Zn(II) Bla2 (ZnZn-Bla2) was unstable. However, di-Co(II) Bla2 (CoCo-Bla2) was substantially more active than the mono-Co(II) analogue. Further, Co(II) binding to Bla2 was found distributed, while Zn(II) binding sequential. These results demonstrated that Zn enzyme binds Co(II) and Zn(II) via distinct mechanisms, underscoring the need to demonstrate transferability when extrapolating results on Co(II)-substituted proteins to the native Zn(II)-containing forms [25].

Metallo-beta-lactamases are are bacterial Zn(II)-dependent hydrolases capable of hydrolyzing all known classes of beta-lactam antibiotics, rendering them ineffective. These enzymes can be subdivided into three subclasses (B1, B2 and B3) that differ in their metal binding sites and their characteristic tertiary structure. BcII is a B1 metallo-beta-lactamase which is found in both mononuclear and dinuclear forms. The position of Zn2 has been reported as essential for a productive substrate binding and hydrolysis [26]. Co(II)"BcII hydrolyzed â-lactam imipenem (both the mono- and dinuclear forms) and the intermediate formed was a metal-bound anionic species with a novel resonant structure that was stabilized by the metal ion at the DCH or Zn2 site [27].

2.5 Cephalosporins: Cephalosporins inhibits the synthesis of the peptidoglycan layer of bacterial cell walls e.g. lactams. Many drugs possess modified toxicological and pharmacological properties when in the form of metal complexes. Sultana and Arayne reported that interaction of cefadroxil, cephalexin, cefatrizine and cefpirome with essential and trace elements caused antagonistic effect in many cases which was shown by decrease in antimicrobial activity of cephalosporins and MIC values were increased [28.] The complex [Cu(cefotaxime)Cl] was found to have higher activity than that of cefotaxime against the bacteria strains studied under the test conditions, showing that it has a good activity as bactericide [29].

2.6 Glycopeptides: These are peptidoglycan synthesis inhibitors. The monomeric complexes of Fe(III) with small molecules (glycopeptides) related to peptidoglycan monomer structure were prepared and characterized by chemical and physicochemical methods [30]. Complexes of antibiotics with metals are useful in detecting microorganisms, including gram-positive bacteria. The complexes are preferably chelated complexes between a glycopeptide antibiotic and a detectable label comprising a transition or lanthanide metal [31].

2.7 Aurecolic acids: The glycoantibiotic aureolic acid family produced by *Streptomyces species* is comprised of several members with similar structures, including chromomycin A_3 ($ChrA_3$), mithramycin, olivomycin, and variamycin, which exhibit activities toward Gram-positive bacteria, DNA viruses, and tumors. A divalent metal ion, such as Mg , Co , Zn , or Mn is required for aureolic acid to bind to a double helical DNA to form a drug-metal-(DNA) ternary complex which is bound to DNA in the minor groove [2].

One of the major attributes for the biological action of the aureolic acid anticancer antibiotics chromomycin A_3 and mithramycin is their ability to bind bivalent cations such as Mg(II) and Zn(II) ions and form high affinity 2:1 complexes in terms of the antibiotic and the metal ion, respectively. Chromomycin A_3 and mithramycin inhibited enzyme activity of alcohol dehydrogenase with inhibitory constants of micromolar order. The nature of the enzyme inhibition, the binding stoichiometry of two antibiotics per monomer, and comparable dissociation constants for the antibiotic and free (or substrate-bound) ADH imply that the association occurs as a consequence of the binding of the antibiotics to Zn(II) ion present at the structural center. Confocal microscopy showed the colocalization of the

antibiotic and the metalloenzyme in HepG2 cells, thereby supporting the proposition of physical association between the antibiotic(s) and the enzyme inside the cell [32].

The anticancer antibiotic chromomycin A3 (Chro) is a DNA minor groove binding drug belonging to the aureolic family. The effects of spermine on the interaction of 2:1 Chromomycin (Chro)-metal (Fe(II), Co(II), or Cu(II) ion) complexes revealed that spermine strongly competed for the Fe(II) and Cu(II) cations in dimeric Chro-DNA complexes, and disrupted the structures of these complexes. However, the DNA-Co(II)(Chro)(2) complex showed extreme resistance to spermine-mediated competition for the Co(II) cation. Further, a 6mM concentration of spermine completely abolished the DNA-binding activity of Fe(II)(Chro)(2) and Cu(II)(Chro)(2) and interfered with the associative binding of Co(II)(Chro)(2) complexes to DNA duplexes, but only slightly affected dissociation. Additionally, DNA condensation was observed in the reactions of DNA, spermine, and Fe(II)(Chro)(2). Despite the fact that Cu(II)(Chro)(2) and Fe(II)(Chro)(2) demonstrated lower DNA-binding activity than Co(II)(Chro)(2) in the absence of spermine, while Cu(II)(Chro)(2) and Fe(II)(Chro)(2) exhibited greater cytoxicity against HepG2 cells than Co(II)(Chro)(2), possibly due to competition of spermine for Fe(II) or Cu(II) in the dimeric Chro complex in the nucleus of the cancer cells. Such results should have significant relevance to future developments in metalloantibiotics for cancer therapy [33]. The [(Mithramycin)$_2$-Fe(II)] complex exhibited higher cytotoxicity than the drug alone in some cancer cell lines, probably related to its higher DNA-binding and cleavage activity [34].

2.8 Macrolides: These irreversibly block 50s microbial ribosome, inhibit translation of tRNA as well as protien synthesis. Erythrocin has been the only macrolide antibiotic in general clinical use for about 40 years. Recently, a host of new macrolides and related antibiotics have become available, e.g. tylosin, spiromycin, leucomycin, oleandomycin, medemycin, josamycin, and roxithromycin, clarithromycin, azithromycin are the most important among them. The animal specific breeds include tylosin and tilmicosin. Macrolides inhibited bacterial protein synthesis by an effect on translocation and their action may be bactericidal or bacteriostatic. The macrolide antibiotic erythromycin contains two sugar moieties and a hydroxyl groups which potentially can serve as metal binding groups. Iron-erythromycin complex exhibit superoxide scavenging activity[35].

2.9 Lincosamides: These are active against Gram-positive cocci, e.g. *staphylococci*, hemolytic *streptococcus* and *pneumococcus*, and also against *clostridium tetani* and *mycoplasma*, but not against Gram-negative organisms. The mechanism of action involves the inhibition of protein synthesis. For example, Lincomycin is a broad-spectrum antibiotic synthesized by *Streptomyces lincolnensis* that is particularly active against Gram-positive bacteria. It is widely used in human and veterinary applications. Manganese dioxides in soils and sediments could contribute to the decomposition of lincosamide antibiotics released into the environment [36].

2.10 Penicillins: These inhibit synthesis of peptidoglycan and cell wall. Amoxicillin and silver nanoparticles combination resulted in greater bactericidal efficiency on *Escherichia coli* cells than when they were applied separately. Moreover, the bactericidal action of silver (0) nanoparticles and amoxicillin on *Escherichia coli* showed a higher antibacterial effect in Luria–Bertani medium with increasing concentration of both amoxicillin (0–0.525 mg ml^{-1}) and silver nanoparticles (0–40 µg ml^{-1}). Dynamic tests on bacterial growth indicated that exponential and stationary phases were greatly decreased and delayed in the synergistic effect of amoxicillin and silver nanoparticles. In addition, the effect induced by a preincubation with silver nanoparticles results showed that solutions with more silver nanoparticles have better antimicrobial effects [37].

2.11 Quinolones: Quinolones inhibits both the bacterial DNA gyrase enzyme and DNA replication. Quinolones are comprised of a large family of antibacterial agents such as nalidixic acid, perfoxacin, norfloxacin, ofloxacin, and ciprofloxacin. The fluoroquinolones are an important family of synthetic antimicrobial agents being clinically used over the past thirty years. In addition, some fluoroquinolones have been used in the development of anticancer drugs, and others have demonstrated anti-HIV activity. Furthermore, there has been some additional work investigating the effect of metal ions on biological activity. The extent of interaction between new quinolones and metal cations has been described [38]. Results suggested that

garenoxacin should be administered at least 2 hours before or 4 hours after administration of Al-Mg antacid or other cation-containing products [39].

The *in vitro* release of levofloxacin has been reported in presence of metal ions like magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium in simulated gastric juice, simulated intestinal juice and at blood pH. Using BP 2002 dissolution test apparatus at 37°C, the availability of levofloxacin was found to be markedly retarded in the presence of all the metals studied [40].

2.12 Sulfonamides: They are competitive inhibitiors of bacterial enzyme dihydropteroate synthetase, and microbial nuclic acids synthesis was also inhibited along with microbial folic acid synthesis. Quinolinyl sulfonamides, such as *N*-(quinolin-8-yl) methanesulfonamide and *N*-(5-chloroquinolin-8-yl) methanesulfonamide [potent methionine aminopeptidase (MetAP)] inhibitors showed different inhibitory potencies on Co(II)-, Ni(II)-, Fe(II)-, Mn(II)-, and Zn(II)-forms of *Escherichia coli* MetAP, and their inhibition was dependent on metal concentration. X-ray structures of *E. coli* MetAP complex with *N*-(quinolin-8-yl) methanesulfonamide revealed that the inhibitor formed a metal complex with the residue H79 at the enzyme active site; the complex was further stabilized by an extended H-bond and metal interaction network. Analysis of the inhibition of MetAP by these inhibitors indicated that this as a typical mechanism of inhibition for many non-peptidic MetAP inhibitors and emphasized the importance of defining *in vitro* conditions for identifying and evaluating MetAP inhibitors that will be capable of giving information relevant to the in vivo situation [41]. Markus et al reported that significant degree of selectivity can be attained with metal-dependent MetAP inhibitors [42].

2.13 Tetracyclines (TCs): They inhibit binding of aminoacyl-tRNA to the mRNA-ribosome thereby inhibiting translation process which is an inportant step in protein synthesis. Their usage has been limited in recent years because of side effects. The acidicoxy-groups at positions 1, 3, 10, 11, and 12 of TC are the potential metal binding/ chelating site. Recent studies of the mechanism for bacterial resistance of this drug has afforded new insight into rational design of analogues and searching for new analogues of this broad-spectrum antibiotic family, such as the novel 9-glycylamido derivatives the''glycylcyclines,'' for defending bacterial infections. One of the glycylcyclines 9-t-butylglycylamido-minocycline (GAR - 936, tigilcycline) is currently under phase II clinical trials. Antibiotics drugs of the tetracycline family are chelators of Ca^{2+} and Mg^{2+} ions. Tetracyclines coordinate metal(II) ions including Ca^{2+} and Mg^{2+} ions under physiological conditions forming chelate complexes with their ketoenolate moiety at rings B and C. These metal(II) complexes were the biologically relevant molecules conferring the antibiotic character of the drug by inhibiting ribosomal protein biosynthesis in prokaryotes. Evidece suggested that that no other metal ion can compete with Mg^{2+} for TetR/[MeTc](+) complex formation [43].

The beneficial effects of tetracyclines are attributed to their metal complex. Tetracyclines complex with copper acts as antioxidants and anti-inflammatory agents (electron scavengers) by neutralizing the damaging oxygen free radicals produced by the activated leucocytes**.** By combining with the copper, zinc, iron and other trace metal elements in enzymes such as collagenase, tetracyclines inhibited the enzymatic destruction of tissues. On the other hand tetracycline's greater affinity for nucleic acids and lipids than most chelates resulted in a greater inhibition of protein synthesis and microbial growth. Preformed copper-aspirinate would be more effective in the control of inflamation and the preformed copper-tetracyclinate would control the collagen vascular disorders of microbial origin[44].

Administration of certain dietary items (example, milk, containing calcium) or drugs (example, antacids, iron preparations, products containing calcium salts) to patients on tetracycline therapy could cause a significant decrease in the amount of tetracycline absorbed [45]. TCs are highly susceptible to oxidative transformation mediated by dissolved Mn (II) and Cu (II) ions and manganese dioxide under environmentally relevant conditions. The oxidative transformation occurred via different TC structural moieties and reaction pathways when different metal species were involved, leading to complicated product formation patterns. It was also found that Al oxide surfaces promoted the acid-catalyzed isomeration and dehydration of TCs. These findings significantly advances the fundamental understanding of the reaction mechanisms

of TC compounds and provided the knowledge basis for better risk assessment of these compounds in the environment [46]. The fundamental understanding of the reaction mechanisms of TC antibiotics with important metal species in the aquatic environment drovides the knowledge basis for better environmental fate prediction and risk assessment for these biologically active contaminants [47].

Tetracyclines coordinate metal (II) ions under physiological conditions forming chelate complexes with their ketoenolate moiety at rings B and C are the biologically relevant molecules conferring the antibiotic character of the drug by inhibiting ribosomal protein biosynthesis in prokaryotes. The Tet repressor, TetR, is the molecular switch for tetracycline resistance determinants in gram-negative bacteria and controls transcription of a gene encoding the integral membrane protein TetA, which mediated active efflux of a tetracycline-metal(II) cation, [MeTc](+), by equimolar antiport with a proton. Researchers evaluated distinct characteristics of the metal binding by crystal structure determination of TetR/[MeTc](+) complexes and of association equilibrium constants of [MeTc](+) and TetR/[MeTc](+) complexes. Various divalent metal ions bind to the same octahedral coordination site, defined by a histidine side chain of TetR, the tetracycline, and three water molecules. Whereas association constants for [MeTc](+) vary within 3 orders of magnitude, association of the [MeTc](+) cation to TetR is very similar for all measured divalent metals. Taking intracellular cation concentrations into account, it was shown that no other metal ion can compete with Mg(2+) for TetR/[MeTc](+) complex formation [48].

2.14 Rifamycin: Rifamycin antibacterial agents inhibited bacterial RNA polymerase (RNAP) by binding to a site adjacent to the RNAP active center and prevented synthesis of RNA products. Artsimovitch et al proposed that rifamycins function by allosteric modulation of binding of Mg^{2+} to the RNAP active center. It was also concluded that rifamycins do not function by allosteric modulation of binding of Mg^{2+} to the RNAP active center[49].

2.15 Anthracycline: Anthracycline (AC) antibiotics are produced by *Streptomy cesspecies* and exhibit wide spectrum of antineoplastic activity toward both solid and hematologic tumors and cancers. The redox activity of the AC ring plays a key role in the action of these drugs. In addition, the metal ion bound to the 11, 12-b-ketophenolate site is also thought to be involved in some actions of these antibiotics [2]. Doxorubicin[50] is powerful chelators of other metal ions, including Cu^{2+} and Al^{3+}.

Copper-complexation had no affect on the cytotoxicity of the doxorubicin drug suggesting thereby that extracellular as well as intracellular mechanisms may be involved in the development of its antitumor activity [51].

2.16 Streptonigrin: Streptonigrin is a metal-binding quinone-containing antibiotic produced by *Streptomyces flocculus.* A redox active metal ion such as Fe and Cu is required for this antibiotic to exhibit full antibiotic and anti-tumor activities. The implication for the formation of metal complexes of the antitumor antibiotic streptonigrin, which cleaves DNA in the presence of metal ions, has been reported [52]. *In vivo*, metal ions such as Zn(II), Cu(II) and Mn(II) facilitated the initial reduction of streptonigrin to the semiquinone by capturing the semiquinone after streptonigrin reduction by biological reductants.

2.17 Bleomycin (BLM): Bleomycin is a glycosylated linear nonribosomal peptide antibiotic produced by the bacterium *Streptomyces verticillus*. Bleomycin when used as an anti-cancer agent, the chemotherapeutical forms are primarily bleomycin A_2 and B_2. Bleomycin A_2 is used in the treatment of Hodgkin lymphoma (as a component of the ABVD regimen), squamous cell carcinomas, and testicular cancer, pleurodesis as well as plantar warts. Bleomycin was first isolated as a Cu^{2+}-containing glycooligopeptide antibiotic from the culture medium of *Streptomyces verticullus*, and was later found to be the most widely used anticancer drugs. [^{62}Zn] BLM can be used in PET oncology studies due to its suitable physicochemical properties as a diagnostic complex *in vitro* and *in vivo* [53,54].

DNA cleavage by bleomycin depends on oxygen and metal ions, at least *in vitro*. It is believed that bleomycin chelates metal ions (primarily iron) producing a pseudoenzyme that reacts with oxygen to produce superoxide and hydroxide free radicals that cleave DNA. The bleomycin-iron complex was the well-studied example of site-specific, metal-mediated damage to DNA[55]. The bleomycin- mediated cleavage of DNA occurred *via* formation of a ternary complex, DNA-bleomycin-iron.

Further, oxidation of the complexed Fe(II) resulted in a site-specific oxidation of DNA, most probably by the hydroxyl radical [56]. Antitumor properties of bleomycin and several of its metal complexes as well as nucleic acid recognition by metal complexes of bleomycin has been reported [57,58]. Bleomycin (BLM) effectively carries out single-and double-stranded DNA cleavage. Activated BLM (ABLM), a low-spin ferric-hydroperoxide, BLM–Fe^{III}–OOH, is the last intermediate detected before DNA cleavage. The DNA dependence of the ABLM reaction indicated that the involvement of DNA in the transition state for ABLM decay and thus reacted directly with BLM–Fe^{III}–OOH instead of its decay product [59].

2.18 Polyether ionophores

The polyether ionophores (monensin, salinomycin, ionomycin, maduramycin etc.) are naturally occurring antibiotics produced by the soil bacteria strains of *Streptomyces spp*. and are widely applied in veterinary medicine. Besides their well known anticoccidiosis activity against *Eimeriya spp*., this class of compounds possesses well studied antibacterial, antifungal, antimucosal and especially in case of salinomycin – anticancer properties. Scientists have shown that monensins (MonH / MonNa / MonK) formed three types of complex species: $[M(Mon)_2(H_2O)_2]$ (M = Mg, Ca, Ni, Zn, Co, Mn (1)), $[M(Mon)(H_2O)]$ (M = Hg (2)), $[M(MonNa)_2Cl_2]$ (M = Co, Mn, Cu (3)). Sodium salinomycin (SalNa) produces two different complex types of composition $[M(Sal)_2(H_2O)_2]$ (M = Co, Ni, Cu, Zn (4)) and $[M(Sal)(H_2O)]$ (M = Pb (5)), while the known divalent metal compounds of maduramycins (NH_4Mad / MadH) consisted of [M(Mad)Cl] (M = Mn, Co (6)) as a main complex unit [60-63].

2.19 Platinum compounds

The antibiotic activities of Platinum (II) complexes such as Cisplatin has been used as anti cancer agents since long [64,65]. Inside the cell, cisplatin causes platination of DNA, which involves interstrand and intrastrand cross-linking as well as formation of adducts, usually through guanine. Formation of cisplatin DNA adducts causes distortion and results in inhibition of DNA replication [66]. DNA is considered the main biological target of cisplatin. Different strategies have been used to improve efficacy of cisplatin like use of nanotechnology to specify the effect of the drug in the target cells [67].

Platinum complexes with distinctively different DNA binding modes from cisplatin may provide higher antitumor activity against cisplatin resistant cells. The *trans* isomer of diamminedichloro Pt (II) has also been studied, trans DDP offers a different attachment mode with DNA and is used as anticancer drug for cisplatin resistant cancer cells. A series of *trans* piperazine compounds were reported to have significant cytotoxicity against cisplatin resistant cells [68]. Irradiation of cis-platin modified DNA with UV light induced cross-links with the protein HMG, which inhibited RNA transcription [69].

The molecular mechanism of action of an antitumor platinum complex $[PtCl_2(cis\text{-}1,4\text{-DACH})]$ (DACH = diaminocyclohexane) has been reported. The inhibition of DNA polymerization by Pt–DNA adducts could be responsible for markedly different effects of DNA adducts of $[PtCl_2(cis\text{-}1,4\text{-DACH})]$ and conventional cisplatin [70].

2.20 Ruthenium compounds

In recent years, ruthenium-based molecules have emerged as promising antitumor and antimetastatic agents with potential uses in platinum-resistant tumors or as alternatives to platinum. Ruthenium compounds theoretically possess unique biochemical features allowing them to accumulate preferentially in neoplastic tissues and to convert to their active state only after entering tumor cells. Ruthenium complexes with oxidation state +2 or +3 show antitumor activity against metastasis cancers but have minimal effects on primary tumors. Two ruthenium-based drugs, NAMI-A and KP1019, have reached human clinical testing. Some developments in the ruthenium-based antitumor drugs field on mixed diruthenium-organic drugs as metallopharmaceuticals in cancer therapy were described. Novel organic pharmaceuticals-containing diruthenium(II,III) complexes have shown promising antitumor activity for C6 rat glioma - a model for glioblastoma multiforme (GBA) [71]. Other promising ruthenium agents include novel ruthenium compound ONCO4417, and DW1/2 that has demonstrated Pim-1 kinase inhibition in preclinical systems. Further development of these and other ruthenium agents may rely on novel approaches including rational combination strategies as well as identification of potential pharmacodynamic biomarkers of drug activity aiding early phase clinical studies [72].

Imidazolium trans-imidazoledimethyl sulfoxide tetrachlororuthenate(NAMI-A), [ImH][trans-$RuCl_4$(DMSO-S)(Im)], (Im=imidazole; ImH=imidazolium) remains one of the leading ruthenium complexes with the best chances of becoming an anticancer drug [73]. The relative binding of ruthenocene derivatives were very high and even better than hydroxyl tamoxifen which is novel antagonist for estrogen [74]. Galanski and his co-workers studied the anticancer properties of Ru (III) arene complexes [75]. Ruthenocene-cymene complexes have shown to damage DNA by forming monofunctional adducts selectively with guanine bases [76].

Ruthenocene complexes showed antiproliferative effect on the MCF-7 (ER-positive) breast cancer cell lines. Many of Ru complexes exhibit anti-estrogen properties similar to that observed for novel anti-estrogen Tamoxifen [77]. The electrochemistry of $RuL_2(CO)_2Cl_2$ [L2 = 7-amino-6-methoxy-5,8-quinolinedione) and the implications for the formation of metal complexes of the antitumor antibiotic streptonigrin which cleaves DNA in the presence of metal ions were reported [78].

2.21 Organometallics

The first successful application of an organometallic compound as a drug is the anti-syphilis drug Salvarsan in 1910. Some successful examples of organometallic based drugs include the anti-tumor properties of the cisplatin, ferroquine for the treatment of malaria, and the use of radioactive ^{99m}Tc compounds as radiopharmaceuticals. It is believed that proteins could be the biological target of organometallics and researchers have shown that compounds with thiosemicarbazone ligands can bind strongly to human serum albumin [79].

Several organometallic compounds have been found to exhibitant antineoplastic activities.Organometallic compound like Iron (III)-salophene with selective cytotoxic and anti-proliferative properties have been used in platinum-resistant ovarian cancer cells [80]. Complexes of transition metal like iron have shown remarkable anti-proliferative properties [81,82]. Ferrocifenes exhibited anticancer activity against hormone dependent and hormone independent breast cancers [83]. Many organometallic analogues of tamoxifen were used as a vehicle for introducing other cytotoxic agents to the cancer cells [84]. Newly emerging ruthenium(II) organometallic complexes not only bind to DNA coordinatively, but also by H-bonding and hydrophobic interactions triggered by the introduction of extended arene rings into their versatile structures. Intriguingly osmium (the heavier congener of ruthenium) reacted differently with DNA but also produce highly cytotoxic organometallic complexes [85].

2.22 Antimicrobial implants;

Antimicrobial implants represent a preventive method against infection. One of the inorganic antimicrobials Novaron (grade VZ 600) coated at 3.0 MPa to titanium alloy (Ti6Al4V) plates exhibited the antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. These results indicated that there is a possibility of using them not only for clean operations but also for operations with suspected bacterial contamination, such as fixation of slight compound fractures [86].

Fusidic acid is a bacteriostatic antibiotic that is often used topically in creams and eyedrops, but may also be given systemically as tablets or injections. The global problem of advancing antimicrobial resistance has led to a renewed interest in its use recently [87]. Transition metal complexes or salts of fusidic acid, especially the silver and zinc salts were found particularly suitable for topical applicationas as anti-infective agents [88]. The radical scavenging activity of various metallobacitracin complexes was shown to be higher than those of free transition metal ions and metal-free bacitracin. The superoxide dismutase activity of the complex was found to be in the order of Mn(II) > Cu(II) > Co(II) > Ni(II) [89] .

3. Metal complexes and bacterial resistance

An accepted definition of antibiotic resistance as presented in 1998 by the Institute of Medicine is “a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure to antimicrobials [90]. The presence and spread of antibiotic resistance in non-agricultural, non-clinical environments has been reported [91]. Studies have reported the occurrence of bacterial antibiotic resistance due to the use of the same antibiotics in both humans and animals [92]. Further, production of ß-lactamases is the most common mechanism of bacterial resistance[93]. Metal contamination represents a long-standing, widespread and recalcitrant selection pressure

with both environmental and clinical importance that potentially contributes to the maintenance and spread of antibiotic resistance factors [94].

Although overuse of antibiotics in agriculture and medicine seems partially responsible, environmental exposure to heavy metals may also contribute to antibiotic resistance, even in the absence of antibiotics themselves. Data on a series of eight lab-scale activated-sludge reactors amended with Zn and/or a suite of three antibiotics (oxytetracycline, ciprofloxacin, and tylosin), in parallel with unamended control showed that sub-toxic levels of Zn caused increased antibiotic resistance in waste treatment microbial communities at comparatively low antibiotic levels, probably due to developed cross-resistance resulting from pre-exposure to Zn [95].

Researchers have come up with a possible substitute that utilizes the metal gallium to mimic iron needed by bacteria need to survive. Rather than a drug designed to attack the bacteria itself, gallium boosts of the body's own natural defenses by fooling bacteria into thinking they are well-nourished [96]. The prevalence of antibiotic resistance may increase in populations via indirect or coselection from heavy metal contamination. Selection for metal tolerance among sediment bacteria may influence selection for antibiotic resistance differently in sediments than in the water column [97]. Colony forming heterotrophic metal resistant bacteria isolated from the sediments of Sunchon Bay, South Korea exhibited resistance to various heavy metals and also to wide spectrum of antibiotics. Plasmid curing results in loss of antibiotic and heavy metals resistance in some of the isolates confirmed a relationship between antibiotic and heavy metal resistance [98]. Heavy metal pollution contributed to increased antibiotic resistance through indirect selection also [99]. Metal pollution resulted in selective pressure that leads to the development of multiple metal/antibiotic resistance among bacterial populations, probably through horizontal gene transfer [100]. Researchers have obtained single-stranded DNA's (reversible, noncompetitive inhibitors of the metalloenzyme, with Ki and Ki' values in the nanomolar range) that are potent inhibitors of the *Bacillus cereus* 5/B/6 metallo-ß-lactamase. The inhibition patterns and metal ion dependence of their inhibition suggested that the oligonucleotides alter the coordination of the active site metal ion(s) [101].

4. Bacitracin and cell wall biosynthesis

Bacitracin is a metal-dependent dodecapeptide antibiotic excreted by *Bacillus* species, including *B. subtilis* and *B.licheniformis* with a potent bactericidal activity directed primarily against Gram-positive bacteria, such as *Staphylococcus* and *Streptococcu*s, via inhibition of cell wall synthesis. This antibiotic requires Zn^{2+} for its biological activity [102], and has been reported to bind several other transition metal ions, including Mn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}. Bacitracin has also been shown to exhibit an interesting, metal-dependent, particularly Cu^{2+} ion, inhibition toward the growth of the mold *Neurospora* crassa [103].

5. Siderophores and ionophores

Molecular receptors known as siderophores are also polydentate ligands that can selectively bind and transport alkali or alkaline earth metal ions and Fe^{3+}, respectively, across cell membranes and artifcial lipid bilayers (for example, enterobactins, ferrichromes, ferrioxamines). Ionophores are special carrier molecules that wrap around metal ions forming typically 1:1 complex, so they can pass through the membrane by diffusion. These molecules can serve as antibiotics by (a) disturbing the ionic balance across membrane via ion transport (particularly, the transport of alkali and alkaline arth metal ions), such ions through the pores, such as gramicidins, and (c) competing for essential iron in the environment, such as ferrichromes. Gramicidin represents ion channel-forming molecule [helical peptide dimer, hydrophobic outer surface interacts with membrane, carbonyls and nitrogens on inner surface can interact with cations as they pass through, potassium selective: *pore* size and ligands select for K^+. Ionophore antibiotics can disrupt this ionic imbalance by allowing ions to penetrate the cell membrane as ion-ionophore complexes or via the formation of ion channels. Gram-positive bacteria appear to be particularly sensitive to the effect of ionophores perturbing normal ion transport. Iron recognition and active transport relies on the biosyntheses and use of microbe-selective iron-chelating compounds called siderophores. Siderophores and analogs can be used for iron transport-mediated drug delivery ("Trojan Horse" antibiotics) and induction of iron limitation/starvation. Recent extensions of the use of siderophores for the development of novel potent and selective anticancer

agents have been reported [104].

6. Metal complexes as antibiotic mimics/artificial metalloantibiotics

Artificial metalloantibiotics activity mimics antibiotics. Biological macromolecules present in living organisms, like proteins, DNA, have many metal-binding sites. As a consequence, coordination compounds can react with such cellular components, displaying possible toxic effects, or they also may have beneficial applications. A number of reports on the the design and synthesis of metal compounds as potential antibacterial agents (metalloantibiotics) are available in literature.

The results generally indicated that more potent complexes possessed better physical properties and are much more effective as chemotherapy agents than their parent antibiotics. However, the complexes may be toxic at the dose level used to the liver and kidney but can be consider as potential antibiotics drugs after reduction in the level of metal ion which is responsible for the toxicity [105]. Classical examples, like cisplatin, and new examples of Pt and Ru compounds are known to bind to several biomacromolecules in a specific way, and eventually bind at DNA [106,107]. The metal ions can be administered in polymeric microparticles, deformable films or microparticles embedded within deformable films. The metal ions exhibited microbiocidal action to the bacterial pathogens that are the causative agents of periodontal disease [108].

Ternary complex seems worth pursuing as a possible antimicrobial agent candidate. Moreover, as the biological studies showed, both the synthesised complexes and the solutions prepared by mixing the components exhibited the same behavior, thereby, proposing a new, faster and accurate methodology to screen metalloantibiotics prior to synthesis of the complexes. [109]. Metal-mediated inhibition is a viable approach for discovering methionine aminopeptidase inhibitors that are effective for therapeutic application [110].

Cu (hesperetin)$_2$(H_2O)$_2$]nH_2O exhibited growth inhibition of SGC-7901 and HepG2 cell lines with respect to hesperetin and was found to bind DNA in intercalation modes. Further, the binding affinity of complex was stronger than that of free hesperetin [111]. Erythromycin and clarithromycin metal complexes resulted in synergistic effects whereas roxithromycin metal complexes resulted in antagonistic effect [112]. Various factors influencing the stability of fluoroquinolone-metal complexes have been reported [113]. Interaction of cholinesterases with other molecules in neuritic plaques and neurofibrillary tangles mediated by transition metal ions were known to be present in AD pathology lesions [114]. The possibility of designing niobium-based antibiotics which block iron uptake by pathogenic bacteria was discussed [115].

A new synthetic ribonuclease [Tb(L1) (OTf) (OH_2)] (OTf)$_2$·MeCN {L1=2-[7-ethyl-4,10-*bis* (isopropyl carbamoylmethyl)-1,4,7,10-tetraazacyclododec-1-yl] -*N*-isopropyl-acetamide }in which the terbium(III) center is 9-coordinate, with a capped square-*anti*prism geometry effectively promoted RNA cleavage in footprinting experiments, in which binding of the Tat peptide and neomycin B to the bulge region of the TAR stem-loop was confirmed [116].

Researchers suggested the possibility that the scavenging effect of the pirfenidone PFD–iron complex contributed to the anti-fibrotic action of pirfenidone used for treating idiopathic pulmonary fibrosis [117]. Quinolones activity decreased in the environment of certain metal ions by formation of sparingly soluble metal chelates. Fluoroquinolones metal complexes were also discussed in terms of their therapeutic application in terms of the nuclease activity and antibacterial activity [118]. A method was reported for inhibiting microbial growth by administering an effective amount of a silver complex of a N-heterocyclic amine [119]. Some important contributions in the area of synthetic analogues of metallo-beta-lactamases, with major emphasis on the role of dinuclear Zn(II) complexes in the hydrolysis of beta-lactam antibiotics have been reported [120].

Some furanyl-derived sulfonamides behave as bidentate ligands in complexation with cobalt(II), copper(II), nickel(II), and zinc(II) with an octahedral geometry and their *in vitro* cytotoxic properties were reported using brine shrimp bioassay [121]. Researchers have suggested the development of new anti-cancer drugs using chelators and chelator complexes with platinum and other metals, and also new protocols of combinations of chelators with known anti-cancer drugs [122].

Collectively, lewis acidity, flexible coordination numbers and geometries, and fast ligand exchange rates make metal ions particularly, Zn^{2+} well suited to serve as cofactors for catalyzing hydrolytic reactions or enhancing the reactivity of the water nucleophile and stabilizing reaction intermediates [123]. Artificial metalloantibiotics might block iron uptake by pathogenic bacteria, in effect starving them to death. Within the body, iron is present in the form of iron ions with a threefold positive charge (Fe^{3+}) and must always be well "wrapped" to prevent it from reacting with proteins and causing damage. In blood plasma, iron is carried in the "pockets" of the iron transport protein transferrin. It only gets unwrapped once it is inside special cellular organelles.

Further, researchers have shown that transferrin can clump together to form wormlike fibrils[124].

The researchers showed that most of the metal complexes Zn(II), Cu(II), Co(II) and Ni(II) with imidazole derivative were more active than the neat ligand, against *Eschereschi coli, Pseudomonas aeruginosa, Klesbiella pneumonia and Staphylococcus aureus* pected [125]. Short oxo-titanium(IV) bond in bacterial transferring has been reported as a protein target for metalloantibiotics [126]. Nickel and copper complexes of ethambutol having octahedral geometry showed anti-tubercular activity [127].

Researchers reported two qualitative methods for characterizing Au(I)–protein adducts and a photoreactive Au(I) complex that produced a covalent bond between the Au(I) complex and the biomolecule[128]. The palladium(II) and platinum(II) complexes with fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin) showed activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$[129]. Complexes of antibiotics (a polymyxin/colistin/aminoglycoside,) and metals were found useful in detecting bacteria and other biological analytes, particularly Gram-negative bacteria [130]. A solid dosage form of a doxycycline metal complex has been reported [131]. Gentamicin known adverse side effects to the kidney and the inner ear resulted from complex formation of gentamicin with Co, Ni, Cd with square planar arrangement around the metal ions [132].

The toxic side effects of synthetic drugs may, in part, be arising due to their interactions with essential metal ions, especially when the metal ions are administered along with the drug as mineral supplements. Researchers reported the interaction between ranitidine and calcium(II), magnesium(II), and iron(II) ions and between levothyroxine and copper(II) and iron(II) ions at the physiological pH values 1.5, 7.4, and 8.0 and the concentrations of the drugs and mineral supplements used were comparable to those in their usual doses [133]. The possible binding modes between duplex oligonucleotides and metallocomplexes were reported [134]. Scientists have reported the role of metal ions, especially iron, in the action of antibiotics employed in anticancer chemotherapy [135.] Advances in the screening for antiproliferative potential of organotins have been reported [136]. Vancomycin was conjugated to a hydrolysis catalyst (or TACzyme). Targeted hydrolysis by such a conjugate was observed using membranes containing lipid II. MIC-values of targeted hydrolysis catalyst constructs could be modulated by Zn(II) [137].

It has been reported that tungsten compounds mimic the action of insulin in intact cell systems. Low concentration (0.1 mM) of sodium tungstate, tungstophosphoric acid, and tungstophosphoric acid dissolved in 2% DMSO could be the good candidates for *in vivo* investigation of their antidiabetic properties [138]. Synthesis, characterization and cytotoxic activity of gallium(III) complexes anchored by tridentate pyrazole-based ligands has been reported [139]. Ga has been reported as a potentially promising new therapeutic for *P. aeruginosa* infections as it can substitute for Fe in many biologic systems and inhibit Fe-dependent processes [140]. Periodontal disease can be treated by the administration of metal ions, preferably silver ions, to the site where the microorganisms that cause this disease reside. Administration can be to periodontal pockets or adjacent to exposed tooth roots or alveolar bone during periodontal surgical proce dures [141].

The nuclease activity and antibacterial activity of fluoroquinolones metal complexes were compared to free fluoroquinolones [142]. Biomimetic systems containing one or two zinc(II) ions supported by phenolate ligands developed as functional mimics of metallo-beta-lactamase catalytically hydrolyzed beta-lactam substrates, such as oxacillin and penicillin G. [143]. Bismuth-fluoroquinolone complexes have the potential to be developed as drugs against *H. pylori* related ailments [144]. Copper(II) bis-

arginate $[Cu(l\text{-}arg)_2](NO_3)_2$ (1) and [Cu(l-arg)(phen)Cl]Cl (2) as mimics of the minor-groove-binding natural antibiotic netropsin showed preferential binding to the AT-rich region of double-stranded DNA. The complexes with a d-d band near 600 nm displayed oxidative DNA cleavage activity on photoirradiation at UV-A light of 365 nm and at red light of 647.1 nm (Ar"Kr laser) in a metal-assisted photoexcitation process forming singlet oxygen ($^1O_2$) species in a type-2 pathway [145]. $[Cu(arginine)_2](NO_3)_2$ mimics the minor groove binder netropsin by showing preferential binding to the AT-rich sequence of double-strand (ds) DNA showed efficient DNA photocleavage activity [146].

The opportunistic pathogen *Pseudomonas aeruginosa* causes infections that are difficult to treat by antibiotic therapy. This bacterium can cause biofilm infections where it shows tolerance to antibiotics. The novel use of a metallo-complex, desferrioxamine-gallium (DFO-Ga) that targets *P. aeruginosa* iron metabolism has been reported. This complex kills free-living bacteria and blocks biofilm formation. A combination of DFO-Ga and the anti-*Pseudomonas* antibiotic gentamicin caused massive killing of *P. aeruginosa* cells in mature biofilms. In a *P. aeruginosa* rabbit corneal infection, topical administration of DFO-Ga together with gentamicin decreased both infiltrate and final scar size by about 50% compared to topical application of gentamicin alone. The use of DFO-Ga as a Trojan horse delivery system that interferes with iron metabolism showed promise as a treatment for *P. aeruginosa* infections [96]. Iron(III) Schiff base complexes of arginine and lysine as netropsin mimics showed AT-selective DNA binding and plasmid DNA cleavage activity in visible light [147].

Dimers of vancomycin linked by a rigid metal complex, $[Pt(en)(H_2O)_2]^{2+}$, exhibited potent activities (MIC 0.8 ìg/mL, 720 times more potent than that of vancomycin itself) against vancomycin-resistant enterococci ,thereby, suggesting that combining metal complexation and receptor/ligand interaction offers a useful method to construct multivalent inhibitors [148]. A series of Co (II), Cu (II), Ni (II) and Zn (II) complexes of modified mercaptothiadiazole compared to the prepared un-complexed Schiff bases against four Gram-negative, *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi* and *Shigella flexneri*, and two Gram-positive; *Bacillus subtilis* and *Staphylococcus aureous* bacterial strains were reported [149].

Silver nanoparticles coated on common polyurethane foams can be used as a drinking water filter to control bacterial contamination of the surface water. Nanoparticles were found stable on the foam and were not washed away by water. Moreover, morphology of the foam was retained after coating. The nanoparticle bind with the nitrogen atom of the polyurethane foams. At a flow rate of 0.5 L/min, in which contact time was of the order of a second, the output count of *Escherichia coli* was nil when the input water had a bacterial load of 105 colony-forming units (CFU) per mL [150].

Schiff base-derived sulfonamides metal [Co (II), Cu (II), Ni (II) and Zn (II)]complexes showed moderate to significant *in-vitro* antibacterial activity against six Gram-negative; *E. coli, K. pneumoniae, P. aeruginosa, P. mirabilis, S. typhi* and *S. dysenteriae* and four Gram-positive; *B. cereus, C. diphtheriae, S. aureus* and *S. pyogenes* bacterial strains and for *in-vitro* antifungal activity against *T. longifusus, C. albicans, A. flavus, M. canis, F. solani*, and *C. glaberata*. However, the zinc (II) complexes were found to be more active. Some of the compounds also showed significant antifungal activity, and cytotoxic activity against *Artemia salina*. The X-ray structure of 4-[(2-hydroxybenzylidene) amino] benzenesulfonamide was also reported [151].

Several families of individual copper complexes have been studied as potential antitumor agents and these investigations, revealed the occurrence of mechanisms of action quite different from platinum drugs [152]. A method of administering cobalt (III) compound having the formula $CoR^1R^2R^3R^4R^5R^6$ or a salt thereof and an antibiotic compound [Each of R^1, R^2, R^3, R^4, and R^5 is the same or different and includes an N-based ligand donor atom selected from the group consisting of ammonia, primary amine, or secondary amine, or salt thereof. R^6 is a ligand] to a subject diagnosed as needing a broad spectrum antibiotic was reported [153].

A solid dosage form of a metal complex of tetracycline for pharmaceutical administration has been proposed wherein $R_1 = C_l$, $N(CH_3)_2$, or H; $R_2 = CH_3$, H, or CH_2=; $R_3 = CH_3$, H, OH, or absent; and R_4 = OH or H, with the provison that if R_2 is CH_3 and R_3 is H, then R_4 is not OH[154].

Punica granatum L. (Punicaceae) referred to in English as pomegranates, have antimicrobial activity against a range of both Gram positive and negative bacteria [155-159]. The addition of vitamin C markedly enhanced the activities of both pomegranates/Fe (II) and pomegranates /Cu (II) combinations against *S. aureus, thereby,* validating the exploration of pomegranates along with additives such as metal salts and vitamin C as novel antimicrobial combinations [160] .

Mixed antibiotics metal complexes

In vivo evaluation of the biological studies of the mixed antimalarial metal complexes and free ligands showed greater activity against some of the micro-organisms, when compared to the parent compounds. Toxicological studies revealed that mefloquine, chloroquine and Ni(Mef)(CQ)Cl_2 may have affected the plasma membrane integrity of the cells and were toxic to the tissues, while the mixed metal complexes of mefloquine and chloroquine (Co(Mef)(CQ)Cl_2 and Fe(Mef)(CQ)Cl_3) would be a better therapeutic drug for malaria [161].

Mixed ligand metal complexes of chloramphenicol and oxytetracycline prepared by using Ni(II), Co(II) and Fe(III) metal chloride were screened for their antibacterial activity against isolated strains of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia* by using diffusion method. The activity data showed the metal complexes to be more potent antibacterial than the parent drugs against the three species [162].

Some new mixed ligand complexes of type ML'B (M(II)=Mn(II), Co(II), Ni(II), Cu(II) and Zn(II); HL'= o-vanillidene-2-aminobenzothiazole; B= 1,10-phenanthroline) and Schiff base metal complexes of types (ML_2 ") and (M_2L") (HL"= *o*-vanillidene-2-amino-N-(2-pyridyl)-benzene sulfonamide) synthesized and characterized by elemental analysis and spectral (IR, ^{1}H NMR and ^{13}C NMR) studies showed more potent *in vitro* biological activities against bacteria, fungi and yeast activities compared with Schiff base ligands [163].

Stability constant and thermodynamic parameters of Cd^{2+} complexes with sulfonamide (sulfadiazine, sulfisoxazole, sulfamethaxazole, sulfamethazine, sulfathiazole, sulfacetamide and sulfanilamide) as primary ligands and cephapirin as secondary ligand were determined by polarographic technique at pH = 7.30 ± 0.01 and μ = 1.0 M KNO_3 at 250°C. Cd^{2+} formed 1:1:1, 1:2:1 and 1:1:2 complexes [164].

A mixed copper complex with deprotonated nalidixic acid (nal) and histamine (hsm) was synthesized and characterized by FTIR, UV-Vis, elemental analysis, and conductivity. The crystal structure of [Cu(hsm)(nal)H_2O]Cl·3H_2O (chn) showed a pentacoordinated cooper(II) in a square pyramidal geometry surrounded by two N atoms from hsm, two O atoms from the quinolone, and one apical water oxygen. Alteration of bacterial DNA structure and/or associated functions *in vivo* by [Cu(hsm)(nal)H_2O]Cl·3H_2O was demonstrated by the induction of a *recA-lacZ* fusion integrated at the *amyE* locus of a recombinant *Bacillus subtilis* strain. Results from circular dichroism and denaturation of calf thymus DNA (CT-DNA) suggested that increased amounts of copper complex were able to stabilize the double helix of DNA *in vitro* mainly by formation of hydrogen bonds between chn and the sugars of DNA minor groove. Complexes of the quinolone family drugs with copper coordinated to other ammines may be active, even if the nuclease activity is not present as in those complexes with phenantroline [165].

7. Conclusions and perspectives

Research at the interface between chemistry, biology and medicine is providing novel ideas for the design of metalloantibiotics. Several different families of metalloantibiotics and the design and potential utilization of metal complexes as metalloantibiotics mimics for battling pathogenic microorganisms have been described. The action of metalloantibiotics mimics in the whole living organisms are expected to differ in general from the action of non-metal containing agents and may offer unique research, diagnostic, or therapeutic opportunities. Mixed antibiotics metal complexes possessed better physical properties and are much more effective as chemotherapy agents than their parent antibiotics. Metal ions can be administered in polymeric microparticles, deformable films or microparticles embedded within deformable films. Experts are of the opinion that further understanding of the structure, function and mechanisms of the current antibiotic resistance will lead to better design of synthetic/ semisynthetic metalloantibiotics.

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