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Review

DNA-METAL INTERACTION AND THE BIOLOGICAL ACTIVITIES OF METAL COMPLEXES: AN OVERVIEW IN THE LIGHT OF RECENT LITERATURE

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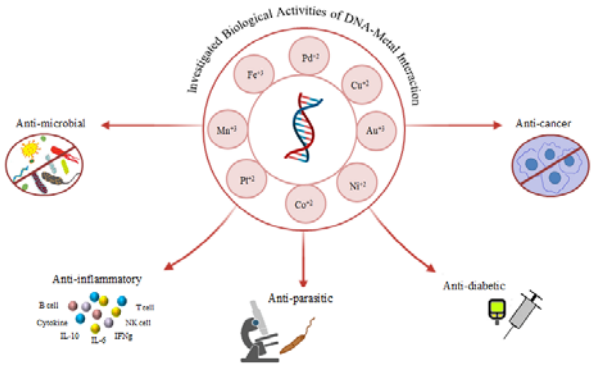
Deoxyribonucleic acid (DNA), which leads the biological synthesis of proteins and enzymes in living cells and carries genetic information, is a potential target for binding many molecules such as metals, metal complexes, anticancer drugs, and some harmful chemicals. Molecules that bind to DNA by covalent or non-covalent intercalation, electrostatic interaction, and groove binding cause disruption in the double-stranded DNA structure. This situation is of great importance in studies conducted in the field of pharmacy to increase the effectiveness of antitumor and antiviral drugs, in DNA-based disease diagnosis and determination of toxicity properties of metal complexes. The purpose of this review is to evaluate the interactions of DNA-metal complexes and provide information about their determined biological activities.



OVERVIEW OF INTERACTIONS BETWEEN METAL COMPLEXES AND DNA

At the present time, studies are carried out to determine the biological activities of many metal compounds and strong evidence is presented for their interactions with the DNA molecule. The discovery of cisplatin, one of the metal-containing compounds that have been widely used, and its success in clinical use have been one of the important developments in the field of health sciences. When it was understood that cisplatin, which is used as an effective anticancer drug and known to bind to the DNA molecule with a covalent bond, has some side effects, researchers turned to the production of new less toxic, and target-specific anticancer drugs.[1] This situation has increased the interest in metal compounds and has paved the way for the use of many metal complexes in the development of new inorganic drugs. In particular, the strong binding of metal complexes, which are used as potential anticancer agents, to DNA in tumor cells, degradation of DNA, and induction of apoptosis are key factors for the development of metal-based anticancer agents.[2,3] The fact that the synthesis of metal complexes is relatively easy and variation can be applied by modifying the ligands or changing the metal center increases the preference in the use of metal complexes.[4] Metal complexes with different geometric structures and various stereoisomeric conformations compared to pure metals have

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provided pharmacological advantages such as organ distribution of formed metallo-drugs and passage through tumor cell membranes.[5] In addition, they are compounds that tend to increase the level of ROS (reactive oxygen species) in cells because they can participate in redox reactions. This allows for apoptosis of malignant tissues, which are known to harbor an impaired redox homeostasis.[6,7]

It has been reported that due to the characteristic geometrical designs and coordinated ligand types of metal complexes, the interactions between DNA molecule and metal-bound various anticancer agents are increased.[2,3] This situation provides an advantage in developing new or effective drug production studies and DNA-based disease diagnoses.[8] For this reason, the determination of the interaction between metal complexes and DNA has gained importance and the studies on this subject have increased. In the studies carried out to date, metal-containing complexes such as platinum, copper, iron, nickel, cobalt, palladium, ruthenium, and zinc have been used in both *in-vitro* and *in-vivo* tests (Table 1). As a result of the researches, it has been determined that metal complexes exhibit different interaction types such as covalent bonding, electrostatic interaction, intercalation, and groove bonding with DNA.[9,10] It has been reported that metal complexes show various biological effects such as anti-cancer, anti-diabetic, antiparasitic, anti-microbial, and anti-inflammatory depending on the binding type and binding potential with the DNA molecule[11]. However, it is observed that the subject is kept up to date due to the intensification of both the synthesis studies of various metal complexes and the studies investigating the cellular resistance mechanism. In this review, we aim to summarize the interaction types between metal complexes and DNA, which are of interest in inorganic chemistry, biochemistry, medicine, and pharmacy, and the biological effects of metal complexes determined by their use in medical biochemistry.

BINDING OF METAL COMPLEXES TO DNA MOLECULE

DNA, which forms the basis of life and carries genetic information, plays a role in the replication and transcription of genetic information and the synthesis of proteins and enzymes in living cells. It is also a potential target for the binding of many molecules.[10] Recognition at the molecular level of the interaction between drugs, molecules, metal complexes, and some harmful chemicals that select DNA as a target, and DNA molecules is of great importance for the determination of possible effects.[12] Particularly in terms of metal complexes, the coordinated water molecules surrounding metal ions can bind to DNA directly or indirectly via hydrogen bonds.[13] In this case, the hydrogen bond between the base pairs (A-G-C-T) located on the inner surface of the DNA double helix and connected to each other by hydrogen bonds is broken and balance disorders occur in the double helix structure.

At the same time, negatively charged phosphate groups are neutralized by the binding of metal ions to DNA.[5-13] This situation may cause some metal ions to affect the DNA synthesis and replication process. This binding results in the unwinding of the double helix and subsequent inhibition of transcription;[14] this results in recognition by DNA damage response proteins and following failed repair attempts, cell-induced apoptosis occurs.[15] Therefore, the biochemical consequences of the interaction between metal ions and nucleic acids have become a reality that should be well known.[16] As a result of the studies carried out to determine the interactions of the DNA molecule with metals and complexes, it has been determined that it has a series of potential interactions such as irreversible covalent bonding, groove bonding, electrostatic interaction, and intercalation between molecules.[9-10-17]

Covalent Binding

Many molecules that interact with DNA in the form of covalent bonding cause apoptosis by inhibiting all events such as DNA replication, transcription, RNA and protein synthesis in the cell.[10] Although the first successful DNA covalent linker to be clinically tested is Cisplatin, the interaction method of anticancer drugs with DNA is generally in the form of irreversible covalent bonding, as in Figure 1.[18,19]

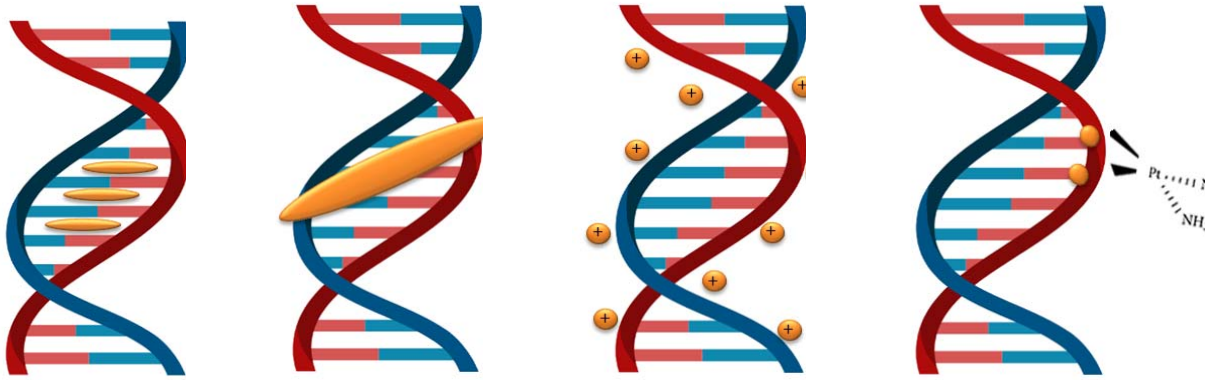
Electrostatic Interaction

The DNA helix proposed by Watson and Crick[20] and still up to date carries negatively charged phosphate groups on its outer surface which affects its functions and structure. As shown in Figure 1, positively charged ions can bind to these negative ions forming the DNA backbone by electrostatic interaction. Electrostatic interactions between DNA and small molecule structures are weaker than other types of interactions. When the molecules are attached to the DNA double helix by external bonding, they remove the ions on the opposite strand and may cause a slight separation in the DNA structure.[21]

Table 1
Evaluation of recent DNA-metal complex studies

Metals investigated for interaction with DNA	DNA Type	Identified Interaction	Ligand Type	Identified Biological Effect	Reference
Cobalt (II) Nickel (II) Copper (II)	ct-DNA	Intercalation	2- (5- (triflorometil)-2-metoksifenilimino) metil) -4,6-diklorofenol and 2- (5- (triflorometil) -2-metoksifenilimino) metil) -4-bromo -6-metoksifenol	Antitumor activity in *in-vitro* cytotoxicity (Hela and A549 cell lines) assays	Jyothi *et al*.[2]
Cobalt (II) Nickel (II) Copper (II)	ct-DNA	Electrostatic interaction or Groove binding	2-(4-sülfametazin)hidrazono-5,5-dimetilsikloheksan-1,3-dion	Successful binding of all investigated metal compounds with DNA and promising results in terms of antioxidant and antimicrobial effects	Kiwaan *et al*.[84]
Palladium (II)	pET21 plasmid DNA	Intercalation	2,2′- bipyridine 5,6-dimethyl-1,10-phenanthroline tetrazole-5-thiol	Investigated complexes bind to DNA and act as binding agents and have weaker DNA binding ability compared to cisplatin	Fatahian-Nezhad *et al*.[85]
Copper (II)	pBR322 plasmid DNA and ct-DNA	Intercalation or Electrostatic interaction	1-methyl-l-tryptophan	The complexes have affinity for DNA and may be potential agents in the production of chemotherapeutic drugs.	Baskaran *et al*.[86]
Copper (II) Iron (III) Palladium (II)	PcDNA3.1 (-) plasmid DNA	Groove binding	Schiff bases of 2-hydroxy-1-naphthaldehyde and Schiff bases of 4-amino-acetophenone	Potential agents in the development of chemotherapeutic drugs	Kurt *et al*.[87]
Copper (II)	ct-DNA	Minor groove binding	Esculetin	Strong photodynamic therapy potential of the Cu-esculetin complex	Shinde *et al*.[88]
Cobalt (II) Nickel (II)	ct-DNA and pBR322 DNA	Intercalation	p-tolylmethanamine Schiff bases	Strong antibacterial and high antioxidant capacity Potent research value	Shankar *et al*.[89]

Cobalt (II)	Herring sperm DNA (HS-DNA)	Intercalation	Benzophenone benzoyl hydrazone ligand (HBBH) and Benzophenone salicylylhydrazone ligand (HBSH)	High DNA binding power Strong antioxidant effect against O2- radical Potential to contribute to new metal-based drug designs in preventing acquired resistance to platinum complexes used in some tumor treatments	Li *et al.*[90]
Copper (II) Platinum (II)	ct-DNA and pBR322 plasmid DNA	Intercalation	2-((2-(pyridin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolone	Inducing cell apoptosis Effective on apoptosis by changing intracellular ROS and Ca+2 levels. A potential agent in the development of anticancer drugs	Li *et al.*[91]
Cobalt(II) Nickel(II) Copper(II)	ct-DNA and pUC-19 DNA	Intercalation	5-methyl-2-phenyl-1,2-dihydro-3H-pyrazole-3-one and 3-methyl-1-phenyl4-[(E)-phenyldiazenyl]−4,5-dihydro-1H-pyrazole-5-ol	Interaction with DNA and antibacterial activity in complexes formed using azo dye ligand The DNA binding constants of the complexes are Copper-Cobalt-Nickel, respectively.	Kirthan *et al.*[92]
Iron (III)	ct-DNA	Intercalation	1-amino pyrene and 2- hydroxy-1-napthaldehyde	Potential fluorescence quencher for DNA-targeted drugs.	Saha *et al.*[93]
Palladium (II) Vanadium (II) Silver (I)	ct-DNA	Intercalation	1-(Pyridin3-yliminomethyl)-naphthalen-2-ol (HNAP)	Potential cytotoxic efficacy on human colon carcinoma (HCT-116), breast carcinoma (MCF7), and hepatocellular carcinoma (HepG2) cells	Abu-Dief *et al.*[94]



(a) (b) (c) (d)

Fig. 1 – Interaction types of DNA and metal complexes
(a): intercalation, (b): groove binding, (c): electrostatic interaction, (d): covalent binding.

Intercalation

Intercalation is defined as the insertion of various molecules between the base pairs of DNA (Figure 1) and occurs without being associated with the base sequence in the helical structure.[10] This type of interaction, which causes the length of the DNA molecule to lengthen and decrease its torsion, disrupts the continuity of the helix structure. Substances that bind with DNA in this type can be monitored by various methods such as UV-absorbance and fluorescence spectrophotometry after their interaction with DNA, due to their structures and intercalation abilities, and play an important role in designing intercalator-based anticancer agents. Ethidium bromide, acridine orange, and phenanthridine can be given as examples of such intercalators.[22]

Groove Binding

The binding of molecules that can enter the grooves in the structure of the double-stranded DNA molecule to DNA by hydrogen bonding or Van der Walls interaction is explained as groove binding.[23] While most small molecules prefer to interact with small grooves of DNA, large molecules (such as proteins and oligonucleotides) usually bind to large grooves.[24] Most of the molecules that bind to the small grooves bind to the A-T ratio-rich sequences. Groove binding, shown in Figure 1, does not produce major conformational differences in DNA. However, some groove binders with small molecular structures can act by inhibiting transcription factors.[25,26]

INVESTIGATED BIOLOGICAL ACTIVITIES OF METAL COMPLEXES

Metal ions play an important role in metabolic reactions in all living organisms. For instance, Na^+/K^+ pump in the transport process across the cell membrane, Zn^{2+} and Co^{3+} work as co-factors in enzymatic processes, Fe^{2+}/Fe^{3+} in the hemoglobin-iron complex facilitates the oxygen transport process, etc.[1] Moreover, divalent cations are also required for the replication, transcription, and translation of the genetic code.[27] Metal ions are also involved in stabilizing the DNA structure by coordinating the phosphodiester backbone of DNA.[28] The interest in metal ions, which are also physiologically important, has increased after the discovery of the anticancer properties of cisplatin. In this context, various metal complexes for medical use have been emphasized and it has been determined that they have different biological effects.

Anti-cancer Effects of Metal Complexes

The use of metal complexes in the treatment of cancer cannot be neglected. Metal complexes, precisely platinum (II) complexes since long are used in chemotherapy and cisplatin have demonstrated high chemotherapeutic potency among this group of metal complexes.[29,30] Cisplatin causes distortion and inhibition of DNA replication via the formation of cisplatin-DNA adducts which usually occur on the guanine portions of DNA since it is the electron-rich site thus, easily oxidized.[31] The formation of cisplatin-DNA adducts is essential as it serves as a binding

site for high-mobility group protein (HMG-protein). The binding of HMG-protein to the cisplatin-DNA adduct has been suggested to contribute to the anticancer effect of cisplatin.[32] Pd (II) and Pt (II) complexes synthesized using ligands such as; glycine derivatives, propyl derivatives, and folic acid showed moderate cytotoxicity against breast cancer cell lines when their activity was compared to cisplatin.[33] Just as other anticancer drugs platinum-based anticancer drugs precisely cisplatin does face drug resistance which is a pressing problem in cancer chemotherapy. Resistance to its effect occurs in about 20% of patients with metastatic cancer.[34] Due to the drug resistance and cytotoxicity of platinum (II) complexes including cisplatin to normal cells, strenuous efforts have been made to improve their efficacy by increasing their specificity to tumor cells via conjugation to molecules like porphyrin.[35]

However, platinum complexes with their DNA binding mode different from that of cisplatin have been suggested to be very beneficial in the treatment of cancer since they exhibit anticancer activity against cisplatin-resistant cancer cells. For instance, trans-diaminedichloroplatium (II) (DDP) has been demonstrated to have anticancer activity against cisplatin-resistant ovarian cancer cell lines.[36] Regarding this, the clinical use of cisplatin is limited and as a result, new platinum-based anticancer drugs such as oxaliplatin, carboplatin, and nedaplatin have been synthesized.[30] In addition, alternative compounds such as organometallic compounds, iron (III) salophen with selective cytotoxicity, and growth-suppressive or antiproliferative effects can be used in the treatment of platinum-resistant cancer cells and this has been demonstrated *in-vitro* on platinum-resistant ovarian cancer cell lines.[37]

Other metal complexes like Titanium complexes as well are used in the treatment of cancer. In other words, platinum is not the only metal complex used in the synthesis or making of anticancer drugs.[38] For instance, *Titanocene dichloride* is a Titanium-based known active anticancer drug used in the treatment of breast and gastrointestinal carcinomas.[30] Aside from this, gold complexes also exhibit anticancer properties. These metal complexes manifest their anticancer properties through a mechanism different from that of cisplatin.[30-39] Furthermore, a study conducted by Marcon *et al*.[40] to determine the cytotoxicity and DNA binding properties of gold (III) complexes with bipyridyl ligands on tumor cell lines reported that the gold (III) complexes exhibited relevant cytotoxic effects on the tumor cell lines. Again, when the cytotoxic properties of some gold (III) complexes were studied *in-vitro* via the sulforhodamine B assay on human ovarian cell lines, they showed relevant cytotoxic properties with *IC50* values with the range 0.2-10μM.[41] Also, radiotherapy or chemotherapy carried out in conjunction with gold nanoparticles yields much treatment success as the gold nanoparticles enhance specificity for the treatment target and also enhance DNA damage.[42] Mn (III)-Salen induces apoptosis in human cancer cells. In a study conducted, Mn (III)-Salen instigated the activation of caspase-3/7 and the release of cytochrome-c from the mitochondrial into the cytosol. This implies that Mn (III)-Salen exhibited its anticarcinogenic effect via the mitochondrial pathway. Mn (III)-Salen derivatives induced apoptosis in breast cancer cell lines at *IC50* within the range of 11-40μM thus they can be regarded as novel anticancer agents.[43]

In addition to the above, ruthenium complexes have been reported to have anticarcinogenic properties against human ovarian cell lines. Ruthenium complexes with oxidation states of 2^+ or 3^+ have an anticarcinogenic effect against metastasis cancers (malignant cancers).[30] Metal complexes have anticancer activity and their emergence has contributed enormously to the treatment of cancer or cancer chemotherapy.[38]

Anti-diabetic Effects of Metal Complexes

Diabetes is a chronic disease occurring basically as a result of elevated levels of blood glucose. Since the past few decades, human health and development are increasingly affected by this condition. It is often accompanied by a disturbance in the metabolism of fat and proteins. Blood glucose usually increases due to the failure of the pancreas to produce insulin or due to the inability of the cells to effectively utilize insulin when produced. Generally, there are three types of diabetes namely: Type 1 diabetes which occurs as a result of the inability of the pancreas to produce insulin hence, also known as insulin-dependent diabetes. Type 2 is the second type of diabetes which is mainly due to resistance to insulin by the body cells hence, also referred to as non-insulin-dependent diabetes. The third type of diabetes is gestation diabetes. This type of diabetes occurs during pregnancy and poses the risk of developing type 2 diabetes in the mother and obesity in

offspring.[44] The majority of diabetic cases are type 2 diabetes with a percentage of 95% out of all diabetic cases. It is predicted to grow by 6% every year worldwide and to reach a total of 350 million cases by 2025.[45]

Its treatment currently depends on therapies intended to reduce hyperglycemia in patients together with exercise and diet control. However, the efficacies of these therapies are limited, tolerance to these therapies is limited and also, they have significant mechanism-based negative effects. Thus, the need for alternative approaches is urgent. In the quest for alternative treatment approaches for diabetes, studies and experiments have been carried out and continue to be done. During the struggle for alternative approaches, it was found that metals and their complexes have anti-diabetic effects.[45] According to Rafique *et al.*[30] the administration of vanadium and zinc as inorganic salts has been reported to have yielded a control in blood plasma glucose levels. Vanadium when in the oxidation state 5^+ as vanadate and in the oxidation state 4^+ as vanadyl can mimic the activities of insulin such as triggering the uptake of glucose by cells and glycogen synthesis.[38-46] Also, chromium supplementation significantly improved glycemia among diabetic patients but did not show any effect on the metabolism of glucose and lipid in non-diabetic individuals.[47] Furthermore, a chromium-binding substance occurring naturally as an oligopeptide can stimulate the activity of the insulin-dependent tyrosine kinase of the insulin receptor to enhance the uptake of glucose. Its stimulating ability was reported to be dependent on the content of chromium.[48] Zinc has an insulin-mimetic activity and anti-diabetic effect. Despite this, research regarding the anti-diabetic effects of zinc complexes is little.[45] Zinc intake seems to be associated with the risk of developing type 2 diabetes. A higher intake of zinc probably slightly lowers the risk of type 2 diabetes in women.[49] Adding to this, patients with diabetes type 1 and type 2 were often found to have low blood levels of zinc.[50] This indicates that a negative correlation exists between diabetes mellitus and zinc. Hence, zinc may actually lower the risk of one developing diabetes. In spite of that, they strive for alternative medicines for the treatment of diabetes continues.[51]

Anti-parasitic Effects of Metal Complexes

Metal-based compounds are used in the treatment of important tropical diseases such as Chagas disease, leishmaniasis, and malaria. Approximately, one million people die annually from these vector-borne diseases. Recently, it has been estimated that half the world's population is at risk of contracting these diseases.[52] N-methylglucamine antimonite and sodium stibogluconate are antimony-based drugs used for centuries to treat intracellular parasitic infection *leishmaniasis*.[53] Aside from that, bismuth also has an effective activity against *leishmaniasis*. Arsenic has also been recognized to have potency against *trypanosomiasis*.[11] Ruthenium complexes of clotrimazole have shown effectiveness against *Trypanosoma cruzi*.[54] Copper (II) and gold (I) clotrimazole exhibited significantly higher growth inhibitory activity against *Trypanosoma cruzi* (the cause of chagas disease).[55] Ibandronate metal complexes have also proven anti-parasitic activity against *Trypanosoma cruzi* by catalyzing the generation of free radical species in the parasite.[56]

In the treatment of malaria, the iron chelator desferrioxamine is used[57] and ferroquine has entered phase II of the clinical trials to be accepted as a drug against malaria.[52] Resistance to chloroquine (antimalarial drug) by *Plasmodium* prompted the need for new therapeutic agents. In course of searching for new alternatives, gold and ruthenium complexes of chloroquine were prepared and evaluated to be effective against *Plasmodium*. Gold-chloroquine complex showed effectiveness against two chloroquine-resistant strains (*Plasmodium falciparum* and *Plasmodium berghei*) when it was investigated *in-vivo* and *in-vitro*.[58] In addition, ruthenium-chloroquine complex has also been reported to have been effective against *Plasmodium falciparum* (Chloroquine-resistant strain) when evaluated *in-vitro*. It was found to be 2-5 times effective than chloroquine diphosphate with no sign of acute toxicity.[59] Ruthenium (II) thiosemicarbazone complexes were evaluated *in-vitro* against chloroquine-sensitive *Plasmodium falciparum*, chloroquine-resistant *Plasmodium falciparum*, and *Trichomonas vaginalis*. These compounds exhibited low to moderate anti-parasitic activity with the ruthenium compounds containing p-cymene exhibiting a better activity. The chlorophenyl moiety-containing ruthenium compounds exhibited the highest antiparasitic activity[60] illustrating that chlorophenyl probably has an effect against the inhibition of parasites.

The antiparasitic activity of ruthenium complexes and lapachol has also been investigated

against *Leishmania amazonensis* and *Plasmodium falciparum*. According to the study, lapachol-ruthenium complexes were more potent than the free lapachol and also the ruthenium complexes showed selective antiparasitic activities.[61] Synthesized two dinuclear silver complexes in an *in-vitro* study manifested an extremely high antiparasitic activity against *Trypanosoma cruzi* and three different strains of *Leishmania spp* at an *IC50* below the lower tested concentration (1μM).[62] Rivas *et al*.[63] reported that compounds with electron-withdrawing ligands, higher lipophilicity and contain platinum would cause higher cytotoxicity of *Trypanosoma brucei.*

The recent use of metal complexes-based drugs such as gold-based drugs in the treatment of old ailments mainly, the tropical diseases such as trypanosomiasis, leishmaniasis, malaria and schistosomiasis[64] are clear indications of the relevance and effectiveness of metal complexes in the treatment of parasitic diseases.

Anti-microbial Effects of Metal Complexes

Most of the metals with an anti-microbial efficacy are typically those belonging to the d-block (V, Ti, Cr, Co, Ni, Cu, Zn, Tb, Ag, Cd, Au, and Hg) and some other metals and metalloids from the group 13-16 of the periodic table (Al, Ga, Ge, As, Se, Sn, Sb, Te, Pb, and Bi).[65,66] Metal complexes are used to treat a wide spectrum of pathological disorders including those caused by microbes. Metals like silver are used widely as anti-infective agents. For instance, silver sulfadiazine is used both as an anti-microbial agent and as an anti-fungal agent to prevent bacterial infections during cases of severe burns. Furthermore, a highly fluorinated silver complex (silver(I) tris(pyrazolyl)borates) demonstrated a good anti-microbial efficacy against *Staphylococcus aureus* and its anti-microbial activity was regarded to be better than those of silver nitrate and silver sulfadiazine.[67] 1% silver nitrate ($AgnO_3$) solution is used to wash the eyes of newborns in some countries to prevent ophthalmia neonatorum. Bismuth (antimony-based compound) has anti-microbial activity against *Helicobacter pylori* and thus, relevant in the treatment of ulcers.[38] The metal complex chlorhexidine silver sulfadiazine has shown to be an anti-microbial agent by preventing catheter infection.[68]

Epidemiological and clinical trials data suggest zinc to be beneficial in the treatment of diarrhoeas.[30] Moreover, manganese complexes have anti-fungal and anti-bacterial properties and their growth inhibitory activity against fungi and bacteria is active.[69]. In an *in vitro* study to investigate the anti-bacterial, anti-fungal and amoebicidal activities of platinum group metal chelates, it was reported that the metal chelates had an anti-microbial effect against a wide spectrum of microorganisms and their effect was significant.[70] Metal complexes synthesized with phenolic compounds such as curcumin enhance the anti-microbial effect of the phenolic compound (curcumin). Cobalt-curcumin complex has demonstrated exhibited an enhanced anti-microbial efficacy than both curcumin alone and cobalt alone.[71] Again, Cr^{3+}, Pd^{2+}, and Y^{3+} metal-curcumin complexes have also shown anti-microbial efficacy against *Escherichia Coli*, *Klebsiella pneumonia,* and *Pseudomonas sp*.[72] Nonetheless, ferrous ions, ferric ions complex with syringic acid and syringic acid exhibited anti-bacterial properties but that of the ferrous ions appeared to be better than the anti-bacterial potency of the ferric ions- syringic acid complex and syringic acid.[73] Bismuth, which is a metal known for a good anti-bacterial activity when used to synthesize a complex with norfloxacin, the complex (bismuth-norfloxacin complex) manifested an enhanced anti-microbial activity against *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Bacillus pumilis* and *Staphylococcus epidermidis* than the norfloxacin alone.[74] This enhanced anti-bacterial activity of the complex was probably due to the increased bioavailability of the complex. Pd (II)-tetracycline complex has been reported to have shown efficacy against tetracycline-resistant *Escherichia coli*.[11] Also, a better anti-microbial activity of Co (II), Ni (II), Cu (II) and Zn (II) complexes has been reported by Palaniammal and Vedanayaki.[75]

Anti-inflammatory Effects of Metal Complexes

Metal complexes are used as anti-inflammatory and anti-arthritic agents. For instance, sodium aurothiomalate, sodium aurothioglucose and sodium aurothiopropanol (gold complexes) are used clinically to treat severe cases of rheumatoid arthritis. Angiogenesis may accompany inflammation hence, the use of anti-angiogenesis agents during treatment is necessary. An oxidative injury which occurs as a result of oxidative stress can cause chronic inflammation. In other words,

preventing or mitigating the occurrence of oxidative injury may hamper the occurrence of inflammation. Ruthenium (III)-quercetin complex reduced oxidative stress and oxidative injury to normal levels in both the brain and testis of male rats[76] thus, Ru (III)-quercetin complex manifested an effect against inflammation. Manganese complexes have been used to treat cell and tissue oxidative injuries by acting as a superoxide anion scavenger.[78]

The synthesis and study of metal complexes with anti-inflammatory drugs is a very interesting research area. It is seen as an alternative approach especially for developing new or more effective drugs.[79,80] Therefore, various metal complexes have been preferred in trials to increase the pharmacological profile of NSAID activity and reduce toxicity. While the copper (II) complexes of Diclofenac (2-[2,6-dichlorophenylamino] phenylacetate), one of the widely used NSAIDs therapeutically in inflammatory and painful diseases of rheumatic and non-rheumatic origin, have inhibited inflammation due to the activation of lipoxygenase, and it has an anti-inflammatory profile superior to diclofenac.[81-83] In addition, complexes of Diclofenac (2-[2,6-dichlorophenylamino]phenylacetate) with metals such as Pd(II), Fe(II), Ni(II), and Co(II) were also tested and the complexes exhibited anti-inflammatory activity, lipid It has been reported to provide protection against peroxidation.[83]

CONCLUSIONS

Metal complexes can interact with several binding sites on DNA and cause conformational changes. For this reason, It is very important to determine the interactions of metal complexes with DNA molecules, which are promising for the treatment of various diseases. Because knowing the type of interaction between metal complexes and DNA allows us to understand how metal-containing drugs actually work and what the mechanisms involved are. Regarding metal complexes, many studies are being conducted to increase the chance of success in DNA-based diseases, identify potential metal complex candidates for medical use, design new DNA-targeted metallodrugs, and screen them *in-vitro*. DNA-metal complex interactions, which is a multi-disciplinary field of study, are being investigated in various fields such as inorganic chemistry, biochemistry, medicine, pharmacy, and also materials sciences.

In addition, many metal complexes have been studied due to their positive properties and have been reported to be efficacy in various diseases such as cancer, diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases. Clearly, metal-DNA interactions are critical to interfere with biological processes.

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