ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(6):
Pg. 2014-2038

Application of Coordination Compounds In Drug Development: An Inclusive Review of Antimicrobial, Antifungal, Antidiabetic and Anticancer

YAME W. MATHUBA[1], NYASHA MAKUVE[1]* and THAPELO MANYEPEDZA[1]

Department of Chemistry, University of Botswana, Botswana.
Correspoding author E-mail: makuven@ub.ac.bw

http://dx.doi.org/10.13005/ojc/410615

(Received: August 29, 2025; Accepted: November 25, 2025)

ABSTRACT

Coordination compounds have been successfully investigated for their therapeutic potential within the pharmaceutical industry due to their distinct chemical and physical characteristics. This literature review aims to offer the applications of coordination compounds in antibacterial, antifungal, antidiabetic and anticancer therapies. It explains in detail transition metal-based complexes which have been tested for treating diseases linked to bacteria, fungi, diabetes and cancer. These include silver nanoparticles which have both antibacterial and antifungal activity, platinum and zinc complexes with anticancer activity, and, oxo-vanadium (IV) complexes with is antidiabetic properties. The review provides the key action mechanisms of these complexes and highlights the efficiency and essential advancements within the field. The findings reveal that coordination compounds help enhance drug efficiency, bioavailability, and promote drug specificity. However, gaps still exist as there is little knowledge on the potential transition metals such as scandium and mmetal toxicity has become a major factor which holds back transition metal-based drugs from being approved. This review further points out the need for extensive research on various heteronuclear and polynuclear complexes. This review also emphasizes the need to adopt sustainable methods in synthesis of metal complexes for bio-inorganic applications. The information from this literature review helps contribute to the ongoing research within the drug development field thus offers itself as a foundation for upcoming studies in this promising research.

Keywords: Coordination compounds, Drug development, Antimicrobial, Antifungal, Antidiabetic, Anticancer.

INTRODUCTION

Coordination compounds also known as coordination complexes comprise of a bond between one or more central transition element and a molecule or ion species known as a ligand[1] (Ligands are referred to as Lewis bases as they concede a pair of electrons to empty orbitals of the central transition atom. The central transition element(s) then becomes a Lewis acid, reason being they accept a pair of electrons from ligands. As such, the coordination of the two is sometimes called a Lewis acid-base adduct[2]. The complex may exist in what is called a coordination sphere which may

be charged or neutral. The charge of a coordination sphere may be negative or positive; in both cases the stability of the complex is compromised. As a result, charged coordination spheres are coupled by charged species referred to as counter ions[3]. The number and identity of ligands which are coordinated to a central atom(s) have impactful effects to the coordination compound as they help dictate the stability, reactivity and geometry of the complex. For instance, the geometry of a complex is directly linked to how many ligands coordinated to a central atom, thus the coordination number of a complex. Coordination chemistry just like other disciplines in chemistry has various applications which cut across numerous fields including catalysis, cosmetic industry, pharmaceutical industry, chemical processes such as photosynthesis and drug development just to mention a few[4].

Drug development is a highly authoritative process of finding a possible medication or vaccine for a particular disease, illness or condition[5]. This process involves four major phases, namely the early drug discovery phase, pre-clinical phase, clinical phase and the regulatory approval phase. These phases occur in the above respective order and involve scientific researchers, medical personnel, and national regulatory bodies amongst others. The early drug discovery phase involves a series of steps including the reveal of the area for which the suggested drug is to work onto. It involves also the identification of active compounds including their mechanism of action. This first major step also entails enhancing the properties of the active compound, a step where the science of coordination compounds is very useful. The second phase is the pre-clinical phase where compounds used to make the drug undergo a comprehensive analysis in a lab. Animals are mostly used to check for the safety and efficiency of the drug during this step[5]. The above two phases involve researchers from biology, chemistry and pharmacy. The third phase is the clinical phase which builds onto what was done in the pre-clinical phase. It has four sub-phases, in phase 1 a more exhaustive analysis of compounds used to synthesis the drug is done, in order to establish drug tolerance, efficiency and suggest dosage. Phase 2 involves a comprehensive process of coming up with a working dosage before the drug is offered. A small number of less than a hundred patients are used to implement the three components. To authenticate the medications tolerance, efficiency and dosage the sample number is increased to multiples of a thousand[6]. These steps occur before the medication is approved and medical personnel such as medical doctors are involved. Phase 4 involves proposals to commercialize the medication, after a receipt of regulatory approval for marketing is equipped. Lastly the final major step is the regulatory approval phase. This occurs after a clinical trial for an active medication or vaccine is complete. The data is collected and analyzed by a national regulatory body. It is only after the compounds analyzed pass the testing that the suggested medication or vaccine can be approved for marketing and be used to treat disease, illness or conditions[5].

Although there has been a huge development in epidemiology, there is still a huge population of humans who die from untreated illness, including medication prescription side effects[7]. Diseases such as cancer are on the rise with more complex destructive mechanisms to the human body as human civilization gets more advanced. Diabetes is also another condition which is now becoming more infiltrated into the human population[8]. Microbes inclusive of bacterial species and fungal species are also evolving, thus reproducing new variants which pose significant health risk to human cells. This calls for more specific treatments and therapies.Prescription drugs can sometimes lead to what is known as iatrogenic illness which includes an adverse reaction due to a prescribed drug. Iatrogenic illnesses are the fifth leading causes of death in the world. The reason being that such drugs are not target specific, they affect and cause other numerous biochemical reactions with their own biochemical cascades. As a result, affecting the non-targeted areas of the patient's body[9]. Coordination compounds enhance drugs specificity to the target area, inclusive of improved binding and controlled release are of great application to drug development[10]. Coordination compounds are therefore an applicable measure to reduce the effects of iatrogenic illnesses which results in death. Coordination compounds have unique and distinct molecular structures hence, they have been used in controlling and treating illnesses related to microbial infection and cancer-related illnesses due to their anti-microbial and anti-tumor potential effects[11]. The aim of this review is to present a comprehensive overview of the

present research and investigations on the use of coordination compounds in antimicrobial, antifungal, antidiabetic and anticancer drug development. This review will cut-cross the anti-microbial, anti-cancer, anti-diabetic and anti-fungal applications of coordination compounds.

Coordination compounds in drug development as antimicrobal and antifungal agents

Introduction to antibacterial and antifungal coordination complexes

Antimicrobial resistance is a process by which single-celled organisms such as bacteria, protozoa and fungi undergo an evolutionary process resulting in them becoming resistant to antimicrobial drugs. This process has now become proliferated within single-celled species. This constitutes as a threat to both human, animal and plant life. Over half a billion people are infected by detrimental fungal diseases such as pneumonia and aspergillosis. These infections are caused by fungal species such as the *Aspergillus fumigatus* which is resistant to most antifungal drugs. Henceforth, the production of new and striking curative agents with the use of coordination compounds is an inspiring, industrious endeavor that could help redress this issue. This is because coordination complexes have biochemical qualities which allow them to impede the homeostasis of most microbes.

This chapter focuses on the inherent capacity of coordination compounds on the drug development of antimicrobial agents specifically: copper, zinc, silver, iron, cobalt and ruthenium. It further delves into the mechanism of action of these metal complexes and recent advancements in coordination compounds as antimicrobial and anti-fungal agents.

Silver-Based Antimicrobial Complexes

Silver salts have prehistoric applications within the medical field. It has antimicrobial applications which date back to the early 18th century right through to the 19th century. It was used as an antiseptic in the form of colloidal silver and used to leech burn wounds in the form of its salt silver nitrate. In 1968 the Food and Drug Administration approved a silver complex called silver sulfadiazine (Fig. 1) commercialized as Silvadene. Silvadene is a wide range antibiotic which can also be used to cure burn wounds[12]. Silver complexes have biochemical properties which allow them to act upon microorganism's cells. These include lipophilicity, redox ability, solubility in water and the ability to release Ag^+ ions, the active element. It is these properties that form the basis of action mechanisms by which silver complexes mainly the Ag^+ ions follow[13].

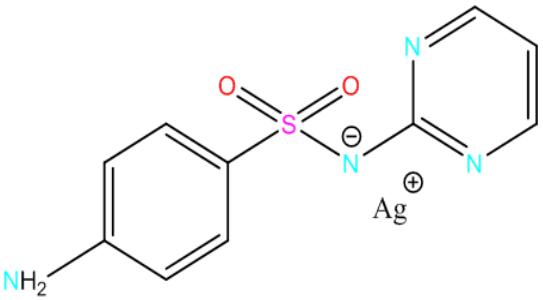

Fig. 1. Silver sulfadiazine structure[13]

Silver nanoparticles (Ag NPs) are antimicrobial agents biologically synthesized. They are of use within medicine due to their explicit action against both fungal species and bacterial species. Savithramma and coworkers prepared Ag NPs from stem bark extracts of *Boswellia ovalifoliolata* and *Shorea tumbuggaia*, and leaf extract of *Svensonia hyderobadensis*. The enclosing of the silver complexes into organic nanoparticles allows for a continuum release of the Ag^+ ions which can infiltrate the cell wall of most single-celled organisms. The bacterial cells have a cell wall, which its main component is a carbohydrate-peptide chain called the peptidoglycan. This is the main target of most antibiotics and thus making it a target of silver complexes[14].

The cell wall also comprises of a bi-phospholipid membrane which is found within the gram-negative bacteria on both sides of the peptidoglycan. The *Gram-positive* bacterium with a much thicker peptidoglycan only possesses a phospholipid bilayer below its peptidoglycan. Ag NPs are of very small size which is about 110nm hence their high tendency to pierce into the cell wall right into the cell membrane due to their lipophilic quality. As such, Ag NPs educe structural abnormalities to both the cell wall and cell membrane as such making the bacterial and fungal cells more susceptible to lysis[12].

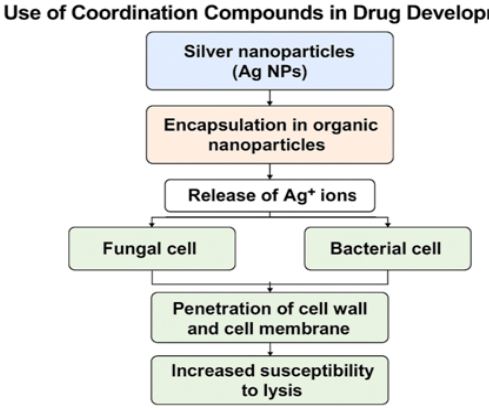

Fig. 2. Mechanism action of silver nanoparticles on fungal and bacterial cells[12]

Escherichia coli, Pseudomonas aeruginosa, Bacillus subtills, Proteus vulgaris and *Klebsiella pneumoneae* were the bacteria species that were cultured and tested for toxicity of Ag NPs. These cultures were spread into a plate containing nutrient agar. They were then exposed to a solution of Ag NPs of 10µg/mL and incubated for 24 h at a temperature of 37°C. The fungal species were also tested for toxicity action by the Ag NPs. These fungal cultures were swabbed on to the potato dextrose agar plates and dipped into a solution of Ag NPs with a concentration of 10µg/mL. They were incubated for 7 days. These fungal species consisted of *Fusarium oxysporum, Curvularia lunata, Rhizopus arrhizus, Aspergillus niger* and *Aspergillus flavus* species[14].

The findings were positive with the effects of toxicity indicated by inhibition zone in millimeters for all bacterial and fungal species. There was great effect among the *Klebsiella pneumoneae, Escherichia coli* and *Pseudomonas aeruginosa* for bacterial species. The inhibition zones were 12mm, 8mm, and 15mm respectively. The Ag NPs were produced from stem barks extracts of *Boswellia ovalifoliolata* and *Shorea tumbuggaia* and leaf extract of *Svensonia hyderobadensis* and this respective order corresponds to the above order of bacterial species[14].

As for the fungal species the stem barks extracts used to produce the Ag NPs were *Boswellia ovalifoliolata* and *Shorea tumbuggaia* and leaf extract of *Svensonia hyderobadensis.* The results were positive for all fungal species. Although, great effect was found within, *Aspergillus niger* and *Fusarium oxysporum* both with an inhibition zone of 10mm because of Ag NPs produced using stem bark extracts of *Boswellia ovalifoliolata*. The Ag NPs produced using stem barks extracts of *Shorea tumbuggaia* showed great effect against the *Fusarium oxysporum* species with an inhibition zone of 12mm. Lastly the Ag NPs produced using leaf extracts of *Svensonia hyderobadensis* were found to have great effect against *Rhizopus arrhizus* with an inhibition zone of 15mm[14].

These complexes have redox ability thus they can release Reactive Oxygen Species (ROS) which can act upon DNA and RNA within microorganisms' cells. DNA molecules are very intrinsic to the survival of microorganisms. It is involved in crucial processes such as the reproduction of daughter cells, transcription for synthesis of messenger RNA which will later be used for translation, a process of protein synthesis[12]. The release of ROS by silver complexes will ultimately prevent DNA replication and as a result cells cannot divide and increase population. Additionally, any disruption to the amino acid sequence of proteins may result in mutations which are detrimental to the normal functioning of the microorganism leading to death.

Young's and coworkers in 2004 prepared some pincer Ag(I)- carbene complexes (Fig. 3) which went through a successful test of their antimicrobial property against *Escherichia coli, Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Compared to the previously used silver nitrate which is not a complex. The silver complex was more effective even at lower concentrations[15]. This has shown promising applications against both bacteria and fungi.

As discussed above, silver has been of use within the medical field for many years, henceforth scientists were interested in preparing complexes of silver. These included the Ag(I) N-Heterocyclic Carbene (NHC) complex which has antibacterial activity. Youngs and coworkers in the year 2004, synthesized various pincer Ag(I)-carbene complexes (Fig. 3) and tested them for toxicity against *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* species. The minimum inhibitory concentration (MIC) of the

complexes with compounds 1 and 2 (Fig. 3) were found to have better antibacterial activity compared to the usually better antibacterial agent $AgNO_3$. This was also evident when lower concentrations of the pincer Ag(I)-carbene complexes were used[15].

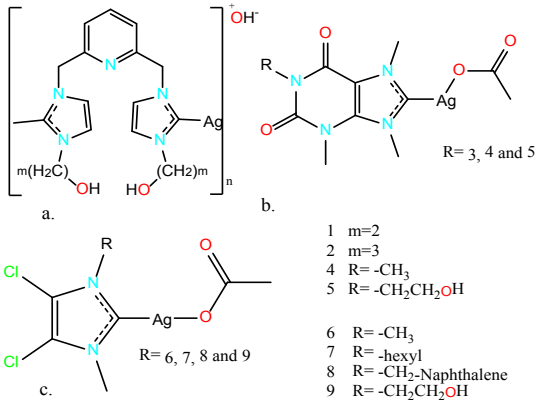

Fig. 3: Silver N-Heterocyclic Carbene complex synthesized by Youngs and coworkers[13]

Various strains of *Burkholderia cepacian*, which is a very resistant respiratory pathogen found within lungs of patients with cystic fibrosis, were inhibited by complex 4 (Fig. 3). Compounds 6-9 (Fig. 3) portrayed MIC values less than 6µg/mL. These were against the *Burkholderia pseudomallei*, *Burkholderia mallei*, *Bacillus anthracis*, and *Yersinia pestis* species. Whereas compounds 4 and 6 were tested against the strains of *Yersinia pestis* and the MIC values were 1µg/mL[15].

Recent investigations show that silver in its first primary valence that is +1 oxidation state, when coupled with antifungal azoles, it has high activity compared to when the antifungal azole is used separately[16]. As for the Ag NPs, when they are combined with some of the general antibiotics and antifungal ligands there is an increase activity seen against the proliferation of both bacteria and fungi[17]. These haven't been officially commercialized; it is as far as the research goes.

Copper-Based Antimicrobial Complexes

Microorganisms use elements such as Carbon, Nitrogen, Oxygen, Phosphorus and Hydrogen in large quantities therefore these are called major nutrition elements. Most transition metals are required by microorganisms in minute quantities therefore known as trace elements. The daily usage of these elements in the human body is less than 100 mg. These include Iron, Zinc and Copper[18]. These transition metals are sometimes referred to as co-factors as they aid in catalytic biochemical reactions by coupling with enzymes. Copper is a cofactor for enzyme superoxide dismutase. They help in affirming the enzyme conformation to accommodate the appropriate substrate[12]. It is important to note that these transition metals including copper are only useful and safe to microbes at low concentrations. At high concentrations they become toxic to microbes, a reason why copper has applicable use in synthesis of antibacterial and antifungal agents. The action mechanism of copper complexes is dependent on their geometry and the type of ligands coordinated to copper[13].

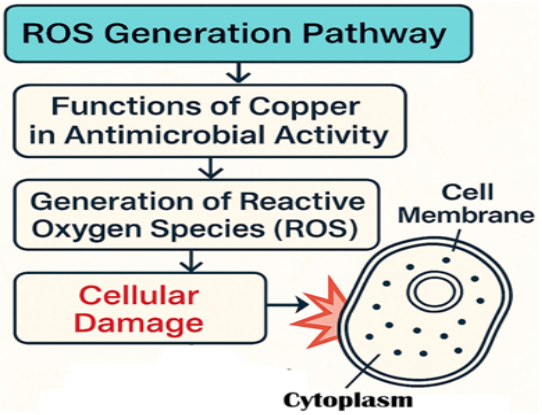

Fig. 4. Mechanism action of copper on bacterial cell membrane[13]

Although the exact mechanism of the antimicrobial activity of copper is not known, many investigations have indicated that it can release Reactive Oxygen Species. These released ROS through the Fenton-type chemical reaction can disrupt the cell membrane of bacteria and fungi. This poses a threat to the genetic material of microorganisms especially the membrane unbound free flowing chromosome of the bacterial species. ROS cause significant damage to the DNA leading to gene loss and ultimately death of microorganisms[19]. A mixed-ligand copper(I) bromide complex with a tetrahedral geometry (Fig. 5), indicated 100 times greater antimicrobial activity against *Escherichia coli, Bacillus subtilis* and *Bacillus cereus*, as compared to ampicillin. It is an antimicrobial agent that uses its ability to release ROS to break down the bacterial cell membrane[12].

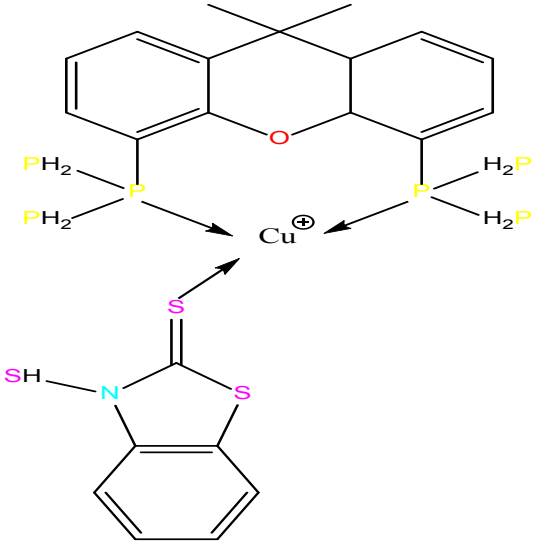

Fig. 5. A mixed-ligand copper (I) bromide complex structure[12]

Another reason why copper complexes are antimicrobial agents is due to their activity when in the form phthalimide-based copper(II) complexes (Fig. 6). Phthalimide moieties and their compounds are known to be antimicrobial due to their ability to euthanize the DNA[13]. The copper complex (Fig. 6) was found to have an antibacterial activity against various strains of bacteria, but this was pronounced within the *Salmonella enterica* with inhibition concentration (IC_{50}) of 0.0019µg/mL. This effect was much pronounced when compared to the commonly used antibiotic ciprofloxacin and the phthalimide ligand itself which is antibacterial[20].

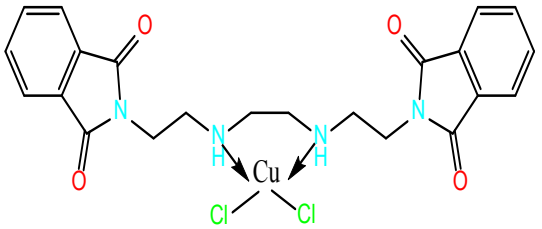

Fig. 6. Phthalimide-based copper (II) complex structure[13]

Copper complexes also help raise the lipophilicity of some compounds which have an antimicrobial activity. Take the case of the free anionic sulphonamides (Fig. 7), which have an antimicrobial activity, but this is hindered by their inability to deeply pierce into the bacterial cell membrane due to low lipophilicity. When sulphonamide ligands are coordinated with copper (II) their lipophilicity is dramatically enhanced. This is due to the delocalization of electrons from ligands to the central atom that occurs within most complexes[12]. Research indicates that copper (II) complexes with five-membered heterocyclic ring substituents such as sulfamethoxazole (Fig. 8) possess greater antimicrobial activity against both *Gram-positive* and *Gram-negative* bacteria as compared to free sulphonamides. This is because they impede the biosynthesis of tetrahydrofolic acid which is essential for bacterial metabolism[13].

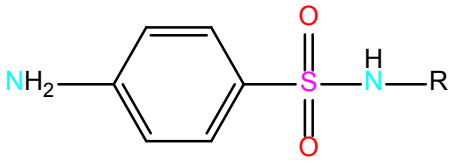

Fig. 7. Free anionic sulphonamide structure[12]

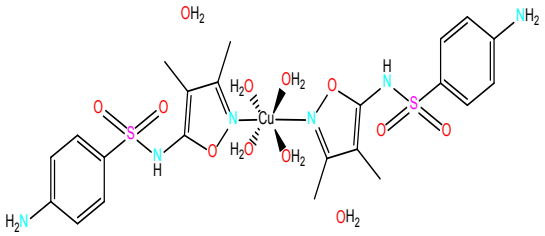

Fig. 8. Copper (II) complex with five-membered heterocyclic ring substituents structure[12]

Currently research on the potential actions of copper-based complexes as antimicrobial is undergoing. Mostly it's the amino acid derivatives, and heterocyclic ligands along with Schiff bases that portray a great activity against both fungal and bacterial species[21]. Copper (II) complexes including the one stated above, along with those coupled to terpene derivatives of ethylenediamine have showed high action against fungal growth when in comparison to standard clinical drugs such as amphotericin[22]. These complexes have also been able to act on bacterial species notorious to be resistant to clinical drugs.

Zinc-Based Antimicrobial Complexes

The second most abundant transition metal in the human body after iron is zinc. An average mass of 2-3 g of zinc is found within the human body. Zinc is another essential trace element which aids in enzymatic biochemical reactions of the human body. An appropriate concentration of zinc enables the activity of antioxidant enzymes such as the zinc-copper superoxide dismutase[23]. Zinc has long been regarded as an antiseptic element. Henceforth, it has been involved in the preparation of drugs with medically active ligands

such as benzimidazole, these giving the complex potentiality to be antimicrobial and antifungal. Zinc inhibits the growth of many bacterial species, for example *Escherichia coli* and *Streptococcus faecalis*. When in its most stable primary valence of +2, its complexes portray antifungal activity against fungal species such as *Candida albicans* and *Aspergillus niger*. Zn^{+2} complexes have around 4 to 10 times higher activity compared to antifungal activities of fluconazole[12]. Zinc complexes antimicrobial activities can be described in two action mechanisms. Firstly, they can directly react with membrane of microbes resulting in loss of membrane structure and thus an increase in membrane permeability. Secondly, they can react with essential molecules such as DNA and RNA. Ultimately the microbes face an inevitable death[13]. These complexes are of a high lipophilic nature, enabling direct interaction and penetration into the lipid membrane as discussed above.

Zinc (II) and Copper (II) ions share similar charge densities and size. Therefore, they have a high tendency to coordinate with identical ligands such as oxygen, and sulfadiazine donor ligands. As a result, some of these metal-based complexes portray similar antifungal and antimicrobial activity. Using the Irving–William's series and the Ligand Field Stabilization Energy, it is clear that the stability of copper (II) complexes is great compared to that of zinc (II) complexes. In general, complex stability increases as the ionic radius decreases across the series. Nevertheless Zn^{2+}, which has lower stability due to the absence of Ligand Field Stabilization Energy for its d10 electronic configuration, is in favor over Cu^{2+}. Reason being Zn^{2+} has no liking for any specific ligand field geometry compared to the Cu^{2+} complexes[12].

This means complexes with unfavorable geometries to metal centers like Cu^{2+} can be synthesized. For example, Abu Ali and coworkers prepared Zn(II) complexes with the anti-steroidal noninflammatory drug Ibuprofen in the presence of N-donor heterocyclic ligands, with various carboxylate coordination numbers (Fig. 9). The crystal structures of the synthesized complexes were determined using a single-crystal X-ray diffraction. Which indicated that the complexes are of different structures and shapes. These included tetrahedral, hexagonal and square planar geometries. Thecomplexes were tested for antibacterial activities against both *Gram-positive* bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*, the inhibition zones found were 10.3mm and 12.0mm respectively using complex 1 (Fig. 9). It was also tested against *Gram-negative* bacteria including *Escherichia coli* and *Klebsiella pneumoniae* with inhibition zones of 14.1mm and 11.3mm using complex 2 (Fig. 9)[24]. The findings indicated a strong influence of the geometry of the complexes on their antimicrobial activities. Additionally, desirable antimicrobial activities, were portrayed by square pyramidal Zn (II) complexes. It had both bactericidal and fungicidal effects against a wide range of bacteria and fungi[12].

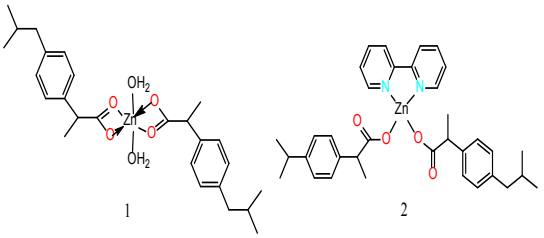

Fig. 9. Structure of zinc–Ibuprofen complexes[12]

Recent studies on zinc-based complexes indicate that there is high activity by zinc metallodrugs on both bacterial and fungal species. Just as seen with silver, zinc can be made into nanoparticles which are efficient against bacterial species such as *Escherichia coli* and *Candida fungal* species[25].

Iron-Based Antibacterial Complexes

Iron is the most abundant transition element in the human body making it an essential trace element required in relatively higher concentration. This is due to its many functions in the human body, primarily the transport of oxygen around the cells of all living things which are dependent on aerobic respiration. Iron as Fe^{2+} forms a complex known as heme in hemoglobin and myoglobin[12]. Enzymes require iron as their cofactor to assist in their function such as the electron transfer property of cytochrome, which is involved in oxidative phosphorylation, a process where large amounts of Adenosine Triphosphate are produced under aerobic respiration[26].

Pathogenic bacterial species depend greatly on iron for their growth, henceforth iron complexes with ligands which have potential antimicrobial activity are of great application within the pharmaceutical industry. Coordinating antimicrobial organic molecules to iron can help

meditate microbial infections. This is due to the efficient drug delivery to the target area property of iron complexes. Iron quinoxaline derivative complexes (Fig. 10) used to treat tuberculosis were synthesized through this strategy which showed an enhanced antibacterial activity of quinoxaline derivatives. The findings were that such iron complexes have a significant enhancement in the activity against *Mycobacterium tuberculosis* as compared to the free ligands. This was achieved by coordinating the quinoxaline derivatives which have antibacterial activity to the iron metal center[13].

For instance, Tarallo and coworkers had synthesized an iron-quinoxaline derivative compounds to as to achieve agents against tuberculosis[27]. The newly prepared iron-quinoxaline derivatives were found to have a significant activity against *Mycobacteria tuberculosis*. The reported MIC values were 3.9-6.2µg/mL compared to that of free ligands which were of 0.78µg/mL. These MIC values range of the iron-quinoxaline derivates is also much greater compared to that of the clinically used antibiotics such as streptomycin and ciprofloxacin which have MIC values of 1.00µg/mL and 2.00µg/mL respectively[28,29].

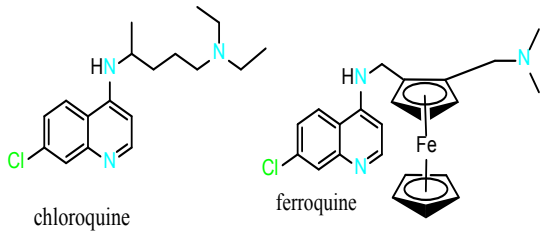

Fig. 10. Structures of chloroquine and iron-chloroquine derivative complex[12]

Iron complexes, with the central metal as Fe^{3+}, effectively carry the bioactive ligands to the target area. It also helps increase concentrations inside the target microbial cells as multiple bioactive ligands can be coordinated to the iron metal center. For instance, iron (III) complexes of 1,2,4-triazole Schiff bases have also been reported to portray greater antimicrobial action against both Gram-*positive* and *Gram-negative* bacteria in comparison to the free bioactive ligands[13]. Although iron is popularly studied in its +2-oxidation state, recent studies have shown that iron in its +3-oxidation state has effective activity against microbes. For instance, iron (III)-based metal-organic frameworks have been proved to be highly antifungal and antibacterial. This is supported by the high inhibition zones and low toxicity when compared to other standard drugs[30].

Manganese-Based Antifungal complexes

Manganese is another essential trace element that is introduced into the human body mainly via food and water intake. This transition element is absorbed into blood via the gastrointestinal tract where it is transported to the mitochondria of different organs such as the liver and pancreas. Just like other transition elements manganese is involved in the activation of many enzymatic biochemical reactions such as of the oxidoreductases[18]. Manganese metalloenzymes include the glutamine synthetase and the phosphoenolpyruvate decarboxylase. The mechanisms of manganese-based complexes against fungal infections include the inhibition of biofilm formation, destruction of fungal essential enzymes and the disruption of metal homeostasis of fungal species.

Fungal cells have sophisticated ways in which they regulate metal homeostasis to help support cellular function and avoid toxicity. Metals such as zinc, iron and manganese are important for various biological processes in fungal cells. They act as cofactors for their enzymes, used in redox reactions and are involved in structural function. Manganese complexes (Fig. 11) on the other hand can segregate essential metals making them inaccessible to fungal cells[31]. This results in abnormal functioning and thus an abnormal growth of the fungal cells. This is due to fact that fungi have enzymes which are dependent on metals as cofactors. Without the metals they cannot carry out effectively biological processes such the DNA replication, respiration and repair mechanisms.

Alternatively, manganese complexes can lead to the increased concentration of manganese metal within fungal cells which is highly toxic to the cells, as it leads to oxidative stress which educe cell death. Reactive oxygen species produced by these complexes cause oxidate damage to essential molecules such the DNA and lipids[31]. This further destroys cell membrane integrity and weakens the cell wall making fungal cells more susceptible to environmental stresses such antifungal agents. An example of such manganese complexes is the manganese (II) based complexes.

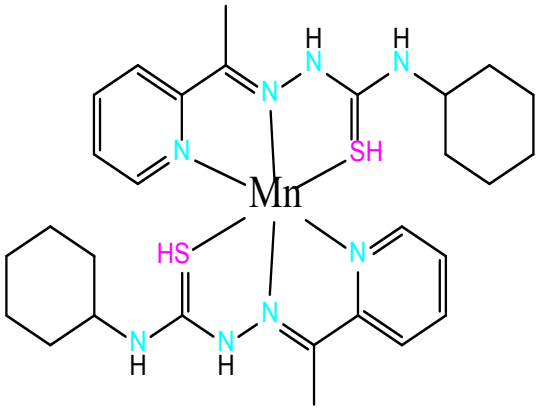

Fig. 11. Manganese based antifungal complex[32]

Manganese complexes have been proven to inhibit the biofilm formation of fungal species. They interrupt the fungal cell's ability to adhere to surfaces and other fungal cells as the extracellular matrix that aids the biofilm is also disrupted. The exopolysaccharides production is also reduced by signal pathways induced by manganese complexes. This is an essential component of the biofilm. Biofilm formation is a way in which fungal cells protect themselves from external harm thus aiding in antifungal resistance but as it becomes inhibited it is much easier to control and treat these fungal infections as the fungal cells are now exposed.

Currently investigation of various new manganese complexes has been used to successfully prove how effective manganese complexes are against both bacterial and fungal species. These novel manganese complexes include the manganese (I) tricarbonyl compounds, which were proven effective against the *Gram-positive* bacterial species, where the cell membrane was disrupted with no effect on human cells[33]. At the same time, manganese complexes have been doped with other metals as a way to reach a wide range of applications across different microorganisms[34].

Coordination compounds in drug development as anticancer agents

Introduction to applications of coordination compounds as anticancer agents

Cancers are a set of ailments which result from the irrepressible proliferation of abnormal cells. These abnormal cells may pervade other normal regions of the body with normal cells thus resulting in what is known as metastatic cancer. This stage is considered the quadrant stage of cancer diseases and may lead to death if the cancer cells are not controlled. There are various causes of cancer, of which there is partial understanding due to their intricate nature. Commonly cancers are caused by a group of substances known as carcinogens which in some way damage the DNA inducing the abnormal multiplication of cells[35]. Examples of carcinogens include tobacco and radiation such as the gamma rays. Factors such as lack of exercise, obesity and dietary factors are known to either prompt or, together with carcinogens they may promote carcinogenesis. Cancer has become one of the world leading causes of death presenting itself as a huge concern in the epidemiology sector.

Coordination compounds have been of huge application in treating and mediating human illnesses and diseases including cancer. Since the discovery of the cisplatin in the year 1965, other transition metal-based complexes have been under investigation to test their antitumor or anticancer potentiality. Transition metal complexes such as platinum, copper, vanadium, ruthenium and copper are examples of complex metals that have been synthesized and tested to develop drugs that are anticancer[19]. This chapter focuses on the inherent capacity of coordination compounds on the drug development of anticancer agents. Precisely gold, platinum, copper and ruthenium. This includes a look at their action of mechanisms, examples of effective complexes and the recent advancements.

Gold-based anticancer complexes

Gold has been of great use in the medical sector since ancient times. Its use can be traced back to Tiongkok in 2500 BC when it was used widely by physicians. It helped treat skin ulcers and smallpox. Some uses also include the use of gold to cure joint pain and mediate illnesses associated with lungs. In 1980 a German bacteriologist Robert Koch discovered that gold complexes can inhibit the growth of bacteria that causes tuberculosis. Although this was proven ineffective later, the effectiveness of gold complexes against rheumatoid arthritis was soon confirmed[36]. Gold therapy soon became popular as now gold complexes are being tested and being used to detect several types of cancer. The reason being that cancer DNA binds to gold regardless of the type of cancer, for example lung cancer (Fig. 12). This is aided using gold nanoparticles.

Nanoparticles are generally less than 100nm in size this is an advantageous property as now researchers can use these NPs to mediate drug development within the pharmaceutical industry. The small size of NPs allows for easy holding of the hydrophobic drugs including the anticancer drugs until they reach their target site with reduced modification by the body immune system. Au-NP have high stability, low cytotoxicity and are biocompatible making them great candidates for drug delivery in anticancer agents[37].

Au-NPs target the tumor cells via accumulation and ensnarement. This is further enhanced and defined by the retention and permeation effect of the Au-NPs into cancerous cells. It is important to note that the level of permeation of the Au-NPs into the tumor cells is more selective towards the tumor cells as compared to the normal cells. This is due to the abnormal characteristic of the lymphatic flow and their angiogenic vessels. The size of Au-NPs allows them to pierce into the cell membrane of tumor cells educing cell apoptosis due to the disruption of the DNA molecule[38]. Additionally, these particles cause a malfunction to the mitochondrial cells thus activating the apoptotic signal cascades within the tumor cells thus leading to cell death.

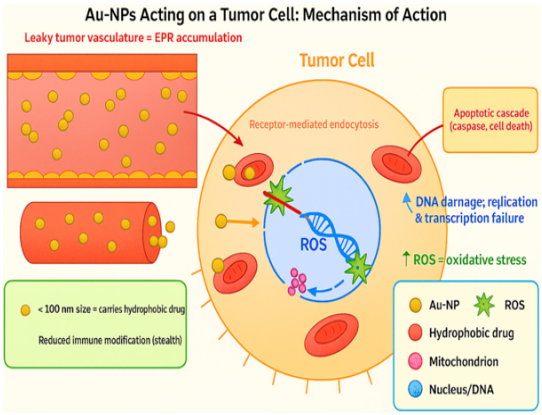

Fig. 12. Mechanism action of gold nanoparticles on lung cancer cells[39]

A study by Dawei and co-workers on the relationship between caspases 3 and 9 activity and the concentration of Au NPs in the presence of substrate p-NA which is fluorescent when catalyzed by caspases at a wavelength of 400nm, revealed that the lung cells exposed to Au NPs of 25 and 50µg/mL indicated a significant enhanced activity of both caspases. The activity of the initiating caspase 3 was more pronounced compared to that of caspase 9. There was a 1.5-fold increase in the activity of caspase 3 treated with 25µg/mL of Au NPs.

The release of Reaction Oxygen Species within cancer cells is enhanced by Au-NPs. This leads to destruction of cellular components such as DNA which are highly essential for replication, that is the proliferation of cancer cells. DNA molecule is also involved in the process of transcription whereby DNA is made into RNA molecule to produce proteins needed by the cell[40]. These proteins include the enzymes which help catalyze biochemical reactions with cells, without them cells are prone to malfunction and ultimately cell death occur. These action mechanisms are similar to most of the gold-based complexes (Figure 13).

Commonly cancer cells are treated using radiation therapy. A process whereby high doses of radiation is used to shrink and kill cancer cells. The radiation source can be from without the body which is known as external radiation. It can also be internal whereby a radioactive species is placed inside or near tumor cells. Au-NPs can act as radiosensitizers, making the cancer cells highly prone to radiation therapy[38]. This is because Au-NPs absorb radiation, therefore if they are placed within cancer cells, they can increase the radiation energy within cells making them more susceptible to death. According to Dewin and coworkers treating the cell with 25 and 50µg/mL concentrations of Au NPs resulted in an increased ROS generation by 50% and 100% respectively. This was successfully identified from DAPI staining.

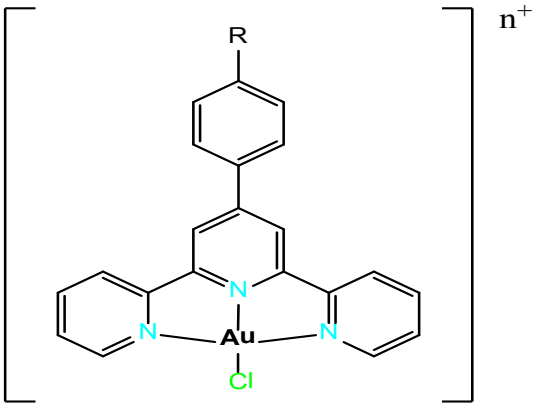

Fig. 13. Gold based complex that has anticancer activity[39]

At the moment there are various investigations ongoing where the gold-based complexes are being synthesized to help enhance

drug delivery. Additionally, this aims to help improve selectivity of drugs for cancer cells as opposed to attacking all rapidly dividing cells such as the hair follicle cells[41]. Most research is within the activity of gold nanoparticles; consequently, functionalized gold nanoparticles are currently used for cancer therapy and theragnostic purposes[42]. These being due to the positive effects of using Au NPs which includes both drug delivery and improved imaging, along side the action of these Au NPs on tumor cells.

Platinum-based anticancer complexes.

Platinum complexes are destructive to tumor cells in the sense that they damage DNA, they are also capable of enhancing the production of reactive oxygen species within a cell thus inducing apoptosis. This is indicated by the cisplatin complex which is an isomer of the Diamminedichloroplatinum (II) (Fig. 14). It is a square planar complex that has been of use in treating cancer since its discovery in the year 1965. It has applications in various cancers including testicular, ovarian and bladder cancer[43]. Cisplatin forms platinum-DNA adducts which interrupt the DNA sequence of cancer cells. This is due to its interaction with the guanine bases within DNA. As it binds to the guanine base it leads DNA damage which have destructive effects leading to cell death. The reason being essential processes such as DNA replication and transcription are inhibited.

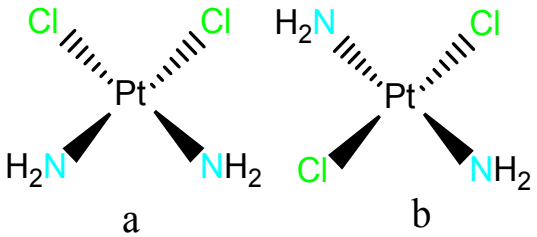

Fig. 14. The structure of a)cis and b) trans Diamminedichloroplatinum (II)[39]

Another platinum-based complex known as Oxaliplatin (Fig. 15) has useful applications in mediating cancer diseases. This is due to its ability to induce the programmed cell death of cancer cells. Oxaliplatin also binds to the DNA thus changing the DNA sequence. This has effects which are activators of the apoptotic pathways within cells (Fig. 17). It is mainly effective in colorectal cancer treatment[37]. This complex also induces immunogenic cell death of cancer cells thus increasing the immune response of the body. This is done via the release of molecules known as the damage-associated molecular patterns such as ATP and HMGB1 which help the immune system identify and invade tumor cells[43]. Another complex with cytotoxic effects on the cancer cells is the novel cationic platinum (ii) complex (Fig. 16). This complex was synthesized by Rimoldi, and coworkers and it was proven successful as a cytotoxic agent against U87 MG glioblastoma cells[44]. The IC_{50} of 19.85±0.97 μM this complex was even better compared to the cisplatin complex which had an IC_{50} of 54.14±3.19 μM[44,45].

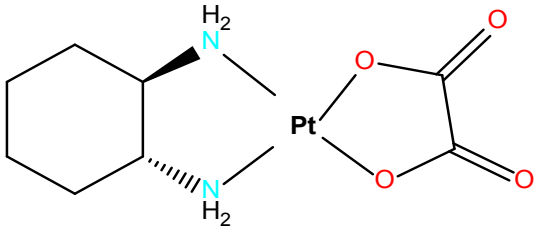

Fig. 15. The structure of oxaliplatin[46]

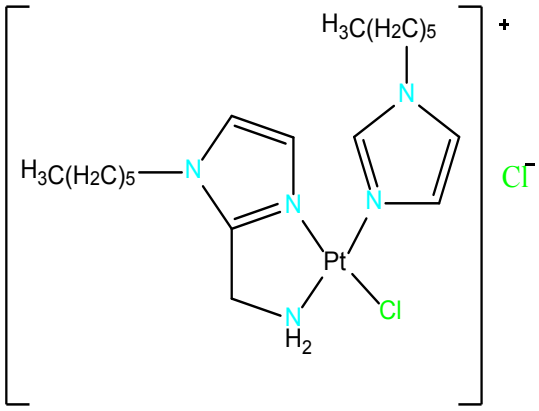

Fig. 16. A novel cationic Platinum (II) complex that is anticancer[12]

Platinum (IV) complexes also offer unique mechanisms which make them key players in treatment of cancer. These complexes are usually reduced to their active form of platinum (II) after they have penetrated the cell membrane of the cancer cells. This process of reducing platinum (IV) to (II) releases reactive oxygen species which contributes to oxidative stress. ROS are highly reactive molecules which can damage the DNA, essential proteins and the lipids with a cell[47]. Additionally, they trigger apoptosis, the reason being the ROS activate signal cascades which lead to the release of cytochrome c from the mitochondria. This activates caspases which are enzymes responsible for apoptosis[48]. Lastly, platinum (IV) complexes can be encapsulated into organic nanoparticles to make Pt-NPs. These have high level of specificity in the sense that they are target specific due to high stability and solubility[11]. This measure also allows for bioavailability of drugs at the target site avoiding

resistance and ensures high concentration of drug at the target site.

Cisplatin has been the first anticancer complex synthesized and used to treat cancer cells. This progressive innovation back in 1965 when it was discovered, but this complex was later deemed highly toxic to human cells. Reason being its lower levels of specificity to cancer cells, rather it invades almost all rapidly dividing cells including some of the human cells such as those in the gastrointestinal tract. Therefore, it has been imperative to synthesize other platinum complexes which are more target specific thus less toxic. Recently platinum complexes have been synthesized such as the platinum (II) complexes with ligands of dithiocarbamate[49]. These have been proved to be less toxic than cisplatin. There is also increased research on how to couple different therapeutic techniques to help reduce the resistance that cancer cells are notorious to acquire[50].

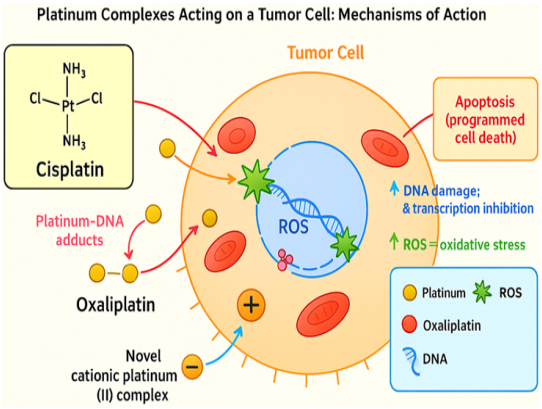

Fig. 17. Mechanism action of platinum-based complexes on cancer cells[47]

Ruthenium-based anticancer complexes

The action of mechanisms of ruthenium-based anticancer complexes varies significantly depending on the geometry and ligands coordinated to the ruthenium complex. Ruthenium complexes usually assume octahedral geometry as compared to the already discussed platinum (II) complexes which assume a square planar geometry. Ligand influences the rate exchange which affects the stability and reactivity of a complex. For high stability to be attained by a complex, there shall be a slow rate exchange, this allows for kinetic stability of a complex as it is able to remain intact until it reaches the target site[51]. Ruthenium-based anticancer complexes interact with the DNA molecule, are highly specific ensuring selective targeting, inhibit metastasis and enhance the generation of reactive oxygen species. The DNA is the target of a family of ruthenium compounds with general formula [Ru(h^6-arene) (N, N^0) X]$^+$. Where X = Cl or I, N, N^0 = ethylenediamine or N-ethyl ethylenediamine. These complexes form either monofunctional adduct or bifunctional adducts with the DNA molecule. Monofunctional adducts occur when a single ruthenium atom binds to one site of the DNA, usually at the N7 position of the guanine whereby ruthenium coordinates with a nitrogen atom. Bifunctional adducts involve the binding of a single ruthenium atom to two sites of the DNA molecule. This creates a cross link that occurs between two guanine bases. This interaction destroys the DNA molecules integrity, henceforth DNA dependent processes such DNA replication cannot occur[39]. The stability and specificity of these adducts is highly dependent on the geometry and types of ligands coordinated to the ruthenium. Ruthenium (II) DMSO-based complexes such the [$RuCl_2$ $(DMSO)_2$ (Hapbim)] do bind to the DNA molecule.

Research conducted by Turro and Sandler indicated that the Ruthenium complexes with an oxidation of +2 are capable of covalently binding with the DNA molecule, specifically the histone proteins after detaching from their ligands[52]. This detachment occurs after the complex is exposed to light irradiation thus allowing the phototoxicity of the ruthenium metal. Turro and coworkers reported that the irradiation of cycloruthenated complexes[53] (Fig. 18) at a wavelength of 690nm influences the toxicity of these complexes on the cancer cells. The IC_{50} value found was 70nM which is 14 times much more than that found when the cells are exposed to a dark environment[53,54].

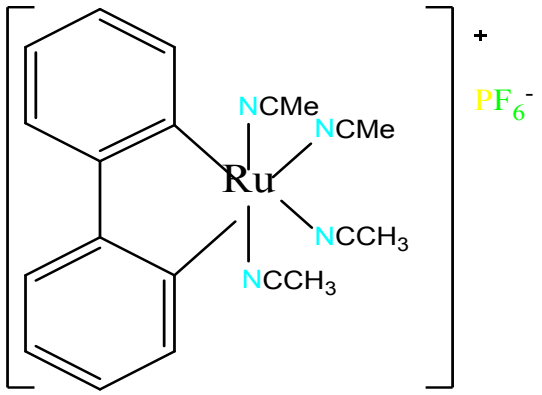

Fig. 18. Example of an anticancer cylcoruthenated complexstructure[53]

Ruthenium complexes such as the tetrachloride dimethylsulpfoxideamidazole ruthenate (III) (NAMI-A) (Fig. 19) have the ability to inhibit

metastasis of cancer cells. NAMI-A inhibits the formation of new blood vessels that tumor cells require to grow and proliferate. Angiogenesis is inhibited by starving the cells nutrients and oxygen gas which they require to multiply[55]. Another way in which this complex prevents metastasis is by reducing the ability of cancer cells to adhere to one another and reduces their ability to move around. The signal pathways that enable the movement and adherence of tumor cells are interrupted by this complex. Ultimately the cancer cells cannot detach from their primary root or primary tumor and pervade other unaffected cells[55].

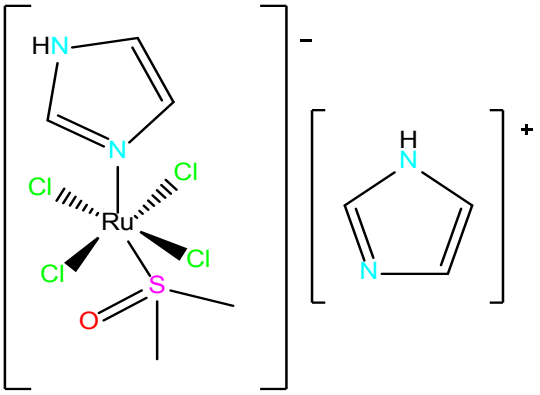

Fig. 19. The molecular structure of NAMI-A complex[55]

There have been multiple studies that involved the synthesis of antineoplastic Ru (III) complexes which have antimetastatic effects to cancer cells such as NAMI-A. This complex has been successfully proven to reduce lung metastasis in mice[56]. A derivative of NAMI-A has also been prepared and this helped boost the activity of the NAMI-A including the stability of the complex when put in solution[57]. The two derivatives of NAMI-A (Fig. 20) were tested for the antimetastatic effects, and the results were of IC_{50} values >200 μM to the human lung cell lines A549[55,58].

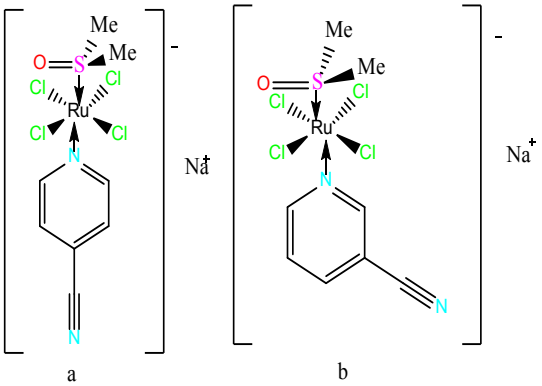

Fig. 20. The structures of NAMI-A derivatives[55]

As of present times there are some ruthenium complexes which are under investigation, being synthesized and some are under clinical trials, for instance complexes such as BOLD-100 and RAPTA-C[59]. Complexes such as the ruthenium (II) polyamine have been proven to have better selectivity and reduced toxicity against prostate cancer cells when compared to cisplatin[60]. There is also growing research on organometallic ruthenium complexes which have mechanism actions that make them potentially, the next-generation cancer drugs[61].

Coordination compounds as antidiabetic agents

Introduction

Diabetes mellitus is a set of metabolic illnesses which are defined by high levels of glucose in blood which is as a result of abnormalities in insulin secretion and or action[8,62]. Insulin is an anabolic hormone which means it is highly involved in the synthesis of proteins, carbohydrates and in the growth of voluntary muscles. Common types of diabetes mellitus include type 1, type 2, and gestational diabetes mellitus[63]. Causes of diabetes are coherent to the type that one has. For instance, poor diet, obesity and genetic predisposition are linked to type 2 diabetes mellitus. When it comes to gestational diabetes mellitus the causes are usually obesity and a family history of gestational diabetes. The causes of type 1 are unknown as of now, but it is linked to genetic factors and environmental triggers such as viral infections[64].

At the moment diabetes mellitus is rising to an alarming epidemic level. In 2014 the World Health Organization (WHO) stated that 8.5% of people aged 18 years and above were infected by diabetes. In 2019, 15 million deaths were due to diabetes with 48% of these people below age 70. Trickle down to 2024 the statistics published by the WHO state that more than 800 million people in the world have diabetes mellitus. Currently there is no cure for diabetes, however, treatment may help manage the disease and if one is lucky, they may reach a stage of diabetes remission. This raises a concern within the medical sector as now the need to develop drugs which are antidiabetic is vital due to the affected population. In recent years, metal complexes have been proved to have antidiabetic properties. These metals include zinc, vanadium, cobalt, copper and triazene-based metal complexes[62]. This chapter focuses on the inherent capacity of coordination compounds on the drug development of antidiabetic agents. Precisely vanadium, zinc, and cobalt. This includes a look at

their action of mechanisms, examples of effective complexes and the recent advancements.

Vanadium-based antidiabetic complexes

Vanadium is a d-block metal which has various oxidation states ranging from -1 to +5. Under physiological conditions the accessible oxidation states include +3, +4 and +5 in the form of V^{+3}, vanadyl (VO^{+2}) and vanadate (VO^{3-}). Vanadium in its +5 state is involved within the extra and intracellular equilibria. The human body has about 50-200 micrograms of vanadium and daily humans take in about 10-60 micrograms through food. Henceforth each organ in the human body has about 0.01-1 microgram. 90% of vanadium in the body is bound to proteins and the rest exists in the ionic form. In 1985, it was found out that vanadium salt namely the sodium orthovanadate when added to drinking water, it can counteract the diabetes symptoms in rats[65]. The action mechanisms of vanadium-based complexes against diabetes include the inhibition of protein tyrosine phosphatase, activation of insulin receptor kinase and it has antioxidant properties.

Vanadium complexes inhibit protein tyrosine phosphatases which are responsible for the dephosphorylating the insulin receptor substrates. This helps in the signaling of insulin as it maintains the phosphorylation state of the insulin receptor substrates. An example of such complex is the Bis(maltolato) oxovanadium (IV) (Fig. 21) which inhibits the PTPs this improving the uptake of glucose and insulin signaling[65,66]. Vanadyl sulfate is an example of a vanadium-based complex that has antidiabetic properties. This is due to its ability to activate the insulin receptor kinase. As it does this, it mimics the action of insulin thus promoting the intake of glucose into cells and the synthesis of glycogen[67].

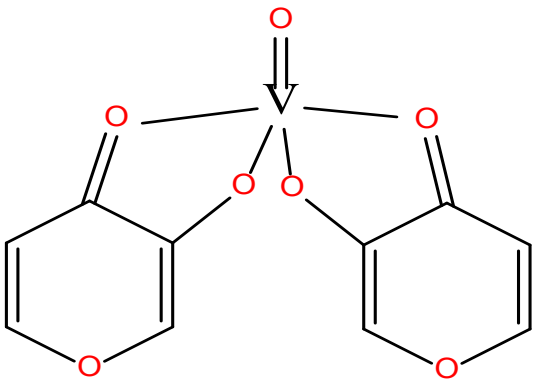

Fig. 21. The structure of the Bis(maltolato) oxovanadium (IV) complex[66]

Patel and coworkers on their research based on the analysis of a mixed ligand oxovanadium (IV) complex with a tridentate Schiff base[68]. The action mechanism of this complex was analyzed using an alpha-glucosidase inhibition assay with an acarbose as the standard. It was then found out that the inhibition activity occurred at a concentration of 200 µM and had an IC_{50} value of 14.75 µM. Compared to the IC_{50} value of acarbose which was 18.59 µM, the complex was said to have moderate inhibition activity[69].

Another action of mechanism portrayed by Vanadium-based complexes is because of their antioxidant property. For instance, the Vanadium (IV) oxide sulphate has exhibited antioxidant properties thus reducing oxidative stress brought about by diabetic conditions[67]. Lower oxidative stress helps preserve pancreatic beta-cells which in turn enhances their function of intaking glucose after meals of high carbohydrates and helps in secreting insulin. These mechanisms help to regulate the concentration of glucose in blood, enhancing insulin sensitivity and as a result they are potential antidiabetic agents.

Currently more vanadium complexes with pincer-type ligands are being synthesized. There has been a novel complex with compounds of dioxidovanadium have undergone preclinical trials where they were proven to be effective drugs for reducing blood glucose concentrations[67]. The challenge that researchers face with vanadium complexes include their high levels of toxicity due to their tendency to accumulate with cells or tissues. This has pushed researchers towards ways in which vanadium complexes can be made less toxic. This has been done via the coupling of these complexes with plant extractions such as the oil from olive seeds[70].

Zinc-based antidiabetic complexes

Zinc is a natural component of insulin; it is essential for the regulation sugar metabolism. It has therefore been proposed to be a new candidate to help in the treatment of type 2 diabetes mellitus along with vanadium[62]. Zinc and diabetes interact at many various points during a cell's metabolism. It has similar effects to that of insulin as it helps enhance the uptake of glucose by the adipose tissue. So much that, deficiency of zinc element in the human body will drastically reduce the intake of glucose

by adipose tissues especially in people affected by diabetes mellitus[71]. Mechanisms of zinc-based antidiabetic complexes include the improvement of insulin signaling, the inhibition of the glycogen synthetase kinase-3β and reduction of oxidative stress (Figure 22).

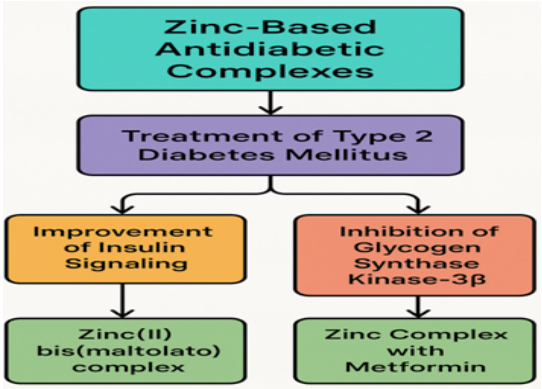

Fig. 22. Mechanism action of zinc-based metallodrugs on diabetic cells[62]

The fact that Zinc has similar actions of insulin means that it can improve insulin signaling pathways. As it activates the insulin receptor kinase along with other downstream signaling molecules. Henceforth, glucose uptake by cells for respiration is increased and the glucose metabolism within tissues is improved. An example of such zinc-based complex is the Zinc (II) bis(maltolato) complex (Fig. 23) which greatly enhances glucose uptake[72]. Zinc complexes also can inhibit the glycogen synthetase kinase-3β. This is evident in the action of a zinc complex with metformin (Fig. 24). This complex has been shown to inhibit the glycogen synthetase kinase-3β, an enzyme which negatively regulates the synthesis of glycogen. When this enzyme is inhibited the synthesis of glycogen is promoted, which will be stores in muscles and liver tissues[71].

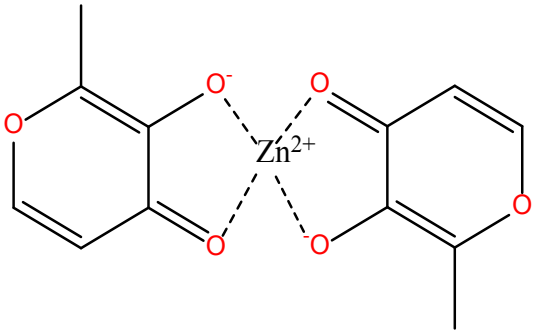

Fig. 23. The structure of Zinc (II) bis(maltolato) complex[73]

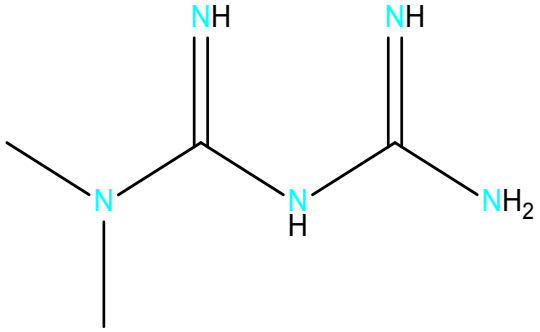

Fig. 24. The molecular structure of metformin[74]

Zinc complexes like vanadium complexes have an antioxidant property which helps to lower the oxidative stress resulting from diabetic conditions. This helps to protect pancreatic beta cells. An example of such a complex is a zinc (II) complex with quercetin (Fig. 25) which has been proven to lower oxidative stress within diabetic cells[62]. Zinc being a popular transition metal with the drug development industry, it is currently being studied to produce other new drugs for treating diabetes. There has been a focus on zinc (II) complexes with organic ligands such as thiazole. These complexes portray great hypoglycemic activity making them promising agents for treating diabetes[75]. However, there are challenges faced with such complexes. For instance, these complexes do not have high stability therefore associated with low bioavailability which if used may lead to resistance with diabetic cells[76].

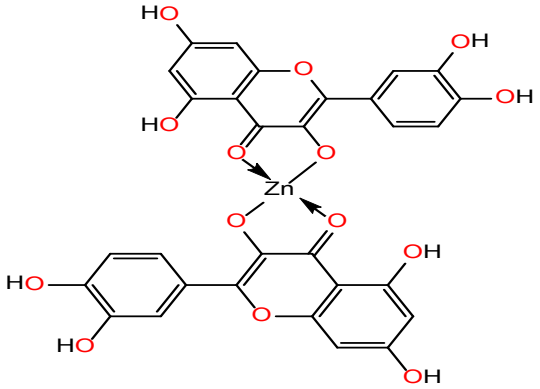

Fig. 25. zinc (II) coordinated to quercetin ligands[77]

Cobalt-based antidiabetic complexes

Among the essential trace elements for animals and humans is cobalt. This element has therapeutic application in the pharmacological field. It is commonly known to exist in the form of vitamin B12 (cobalamin), which is an essential nutrient with vital roles to play within the human body. It is the only metal-containing water-soluble vitamin which

is stored in the liver cells. Cobalamin cannot be synthesized by the human body; it is sourced from the diet[78]. Cobalamin is vital for DNA synthesis and the formation of red blood cells as a result cobalt is used to treat anemia. It has also been found to enhance the effects and the action of insulin henceforth it has applicable uses against diabetes. Cobalt-based complexes help improve the action of insulin due to their ability to enhance the insulin signaling pathways. This is due to the activation of insulin receptor kinase and other downstream signaling molecules involved in insulin signaling. Additionally, they can inhibit the glycogen synthetase kinase-3βwhich leads to the synthesis of glycogen and its storage within the muscle tissues and the liver[79]. For instance, Co(II) complex coordinated to quercetin (Fig. 26) was investigated through an assay of DPPH spectrophotometer. The IC_{50} values from the DPPH assay were found to be 3.88±0.06μM for quercetin and 2.01±0.25μM, for the Co(II) complex[80]. This was taken as evidence that coordinating quercetin to cobalt (II) metal enhances the antiradical characteristics of quercetin.

As of present time, more attention has been drawn to how cobalt nanoparticles could serve as the next-generation agents for diabetic cells. Research indicates that the administration of these cobalt nanoparticles orally, helps to prevent and control within the experimental models. This is due to their ability to improve resistance against diabetes complications. The challenge faced however, is finding a way to prevent the toxicity due to the accumulation of the cobalt nanoparticles as a result of long-term use[81].

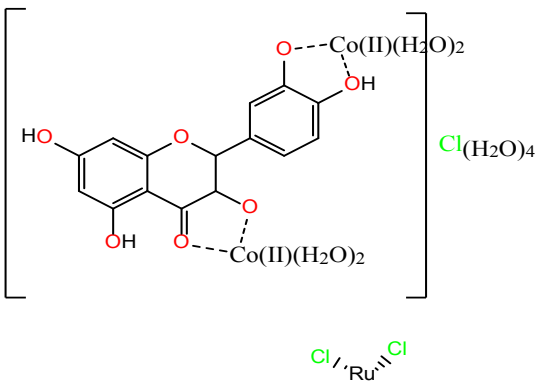

Fig. 26. A structure of a cobalt-based antidiabetic complex[82]

Recommendations

This chapter will point out some of the gaps within this research and as to help provide some recommendations to help close these research gaps. This is an attempt to enhance the development of coordination chemistry as a discipline that is used within medical science via medical chemistry. The suggestions will encompass future perspectives, the drug approval process, sustainability and the economics of drug development using coordination compounds.

Future perspectives

As of now, researchers have been able to synthesize various transition metal-based complexes which can mimic various antimicrobial agents and those which can portray the action mechanisms of essential hormones such as insulin. This led to an increased drug efficiency and heightened specificity towards the target area. For instance, zinc(II) complexes and platinum complexes have been proved in laboratories for their antidiabetic and anticancer action, respectively. Although these complexes have increased heightened the drug efficiency and selectivity, they still have some level of toxicity[83]. There is also a risk of side effects which is because of them affecting untargeted areas within the organism's system. For example, cis-platin which is used as an anticancer agent has been reported to induce side effects such as kidney vomiting and loss in ability to taste food[84]. These side effects are a way in which the body responds to an action of a drug that is affecting other untargeted areas. This calls for the need for researchers and scientists synthesize other complex based drugs which induce no side effects.

Zinc (II)-based complexes have been proven to have successful antifungal and antibacterial effects, as well as anticancer and antidiabetic effects[85]. As much as other transition metals like Vanadium also cut-cross all the four classes of diseases, it is not as much investigated like zinc. This is due to the broader application that has been discovered amongst the zinc element to the human physiology[86]. This means that complexes such as cobalt, copper and vanadium which are of less known application to the drug development process are behind in terms of drug processing compared to zinc elements.Although most of the zinc-based complexes are still under or awaiting the process of approval by the drug administrators. They are much ahead compared to other complex based drugs which have not yet preceded the clinical stages yet[87].

This calls for extensive research and analysis into other transition metals as we cannot heavily and solely depend on one transition metal to try and mediate all classes of diseases.

The economics of drugs.

We live in a socio-economic world where as much as the advancements in science and technology help run our day-to-day lives with ease, there is need to have these inventions bring some income back to the innovators. As such, everything in today's world is eventually monetized. This includes the process of drug development be it with organic, or inorganic compounds. Henceforth, it is vital to take into consideration the economics of coordination compounds in drug development. This is a highly expensive endeavor due to its various sophisticated and highly regulated processes.

Drug development is also a very lengthy process due to multiple stages involved before a drug can even pass approval. It can take up to 14 years and research using articles published from 1980 to 2009 had costs ranging from USD$ 92 million to USD$ 1.8 billion[88]. Comparing these statistics to those of gathered from research done in 2021, there was a rise in the cost which ranged from 161 million USD$ to 4.54 billon USD$[89]. Hypothetically, as of now in 2025 the costs of drug development have skyrocketed especially when dealing with sophisticated diseases such as cancer which already leads in terms of being costly to find potential drugs or vaccines.

Additionally, transition metals unlike organic compounds which can be sourced from living organisms or synthesized. They are most times obtained from within the deep layers of the earth through a process called mining[90]. This is another field which uses highly complex and robust machinery to penetrate the rocky surfaces of the earth henceforth it makes sense that this machinery used is highly expensive. This is another point which adds to the costs involved within drug development[91]. Obviously transition metals are sourced from the ground with some impurities therefore they undergo a series of steps which help remove those impurities, which is another cost. From being mined, these transition metals need to undergo cleaning, cutting and polishing before they can be used[92].

These stages are also expensive and require a lot of precision and accuracy as now the transition elements are in their purest form. As if that is not enough, within the drug development process, there is a stage where the drug after being approved by a national drug administration must be commercialized or marketed. This includes the use of advertisements and the pricing of the drug which also adds to costs of a drug which has not yet been known by its assumed consumers[88]. It is really risky business endeavor which business personnel may not find profitable. With that said, we must mind that these drugs if approved can save a lot of lives including ourselves especially from diseases which are genetically inherited and with unknown causes such as the diabetes mellitus type 1.

Therefore, it is imperative to have an outlet of various stakeholders funding into the pharmaceutical sectors and the biochemistry field where researchers and scientists investigate the potential actions of transition elements against diseases in the laboratories.

Sustainability and Energy conservation

The synthetic process of transition-based drugs have potential harmful effects to the environment revealed through the post-marketing surveillance whereby the safety of the environment is not considered compared to that of the patient[93]. Therefore, the goal is mainly to produce a drug that can cure a patient regardless of the collateral damage done to the environment. A way in which this is done includes the use of hazardous solvents such as dichloromethane, which has been common in the traditional production of complexes[94].

This solvent is used at an industrial level, which if so, it is used in large quantities it can destroy the ozone layer within the lower atmosphere. This is due to its volatile property which can also allow it to enter water bodies such as the oceans where there are marine animals which will take in such a hazardous chemical[95]. This is also a risk to humans who consume marine animals such as fish and via bioaccumulation, they take in dichloromethane at high concentrations leading to other diseases. This is somehow counteracting the goal of the medical sector as they are trying to cure diseases but along the way there is potential to cause other diseases. As it has been discovered that dichloromethane

has carcinogenic potentiality thus proving to be of threat to human life[96].

Another thing to keep in mind is that these processes consume a lot of energy which releases harmful waste products which are non-biodegradable thus poisoning the soil or water bodies if disposed of in local drain systems that reach water bodies. The pharmaceutical industry has been reported to have a significant contribution to the global carbon emission from by 2015 it was found out that pharmaceutical industry's carbon emission increased by 77%[97]. As mentioned above, transition metals are mostly mined and that too has harmful effects on the environment. Mining destroys habitats of animals which live both underground and above ground in the areas being cleared for mining.

There is also an issue of deforestation that occurs when mining occurs this reduces both the animals within an area and the plants which help reduce the accumulated greenhouse gas being carbon dioxide within the atmosphere[90]. This leads to an increased concentration of carbon dioxide in the atmosphere leading to global warming which also has negative effects on both the environment and human beings. The ecosystem is disrupted when plants which animals depend on for both food and habitat are cleared.

This is a serious issue that needs to be resolved as it places not only the planet in adverse conditions but also human beings. This can be achieved using green chemistry, a principle which if the pharmaceutical industry remains committed to will greatly reduce the negative impacts that face the environment[98]. It aims to use biodegradable or environmentally friendly solvents[99]. This also involves the use of patented green tech toolbox which help monitor chemical processes and thus reduce waste production[100]. This has been adopted by companies such as Dude Chem.

Practicing sustainable activities such the use of renewable raw materials can also help to minimize waste and reduce the amount of energy which is consumed by traditional methods. A leading pharmaceutical company such as Pfizer's has adopted such schemes to minimize the negative impacts that face the environment[101]. Pharmaceutical industries can transition metals from environmentally friendly sources such as urban mining and the practice of bio-mining. Urban mining is the reprocessing of already existing materials to source the raw materials which have been used to make such materials[102]. Metals such as iron which are used in building houses and hence when such buildings are no longer of use, they can undergo urban mining. This saves the planet from the effects of afforestation as the area is already available for mining.

Recycling of materials such batteries and electronic waste can help source transition metals such as copper and nickel which are components of these materials[101]. Another useful way is the use of bio-mining, whereby certain strains of microorganisms are used to source transition elements from low grade ores and waste known to contain transition metals. These processes are much friendly to the environment and use less energy compared to the traditional mining[103]. Additionally, they help reduce costs which would have been spent on mining, although they are of no significant cost reduction but accumulatively, they provide a significant gap of reduced costs with less production of waste.

The approval process for transition-based drugs.

It is not common for a patient to be prescribed a transition-based drug; mostly these drugs are of organic molecules. This means that drugs which pass the drug approval stages are mostly organic based as they are ones used in daily life. These common prescription drugs include Acetaminophen commonly known as paracetamol, aspirin, and ibuprofen[104]. Next on the line of being approved are the inorganic-based drugs which contain elements such as magnesium and lithium. For instance, lithium carbonates are used to treat bipolar disorders and magnesium sulphates are common for treating epilepsy[105].

When it comes to inorganic transition metal-based drugs, their approval can be said to move at a snail pace. There are examples of approved transition metal-based drugs used in everyday life. For instance, zinc sulphate, ferrous salts and the popular cisplatin. Reasons why transition metal-based drugs are left pending to be approved is due to their toxicity and the often resistance that is acquired by microbes and cancer cells being targeted[83,106]. This goes out to say although these drugs are of high efficiency compared to commonly

used drugs, they have side effects which are much adverse compared to these common drugs which are mostly organic-based compounds.

This goes out to say that even though there is an increased efficiency, there is need for synthesizing other complex drugs or modifications can be done to the already synthesized drugs. Implementation of various international drug administrations which aim at regulating synthesized and thus proposed drugs across countries can help to facilitate drug development and reduce redundant processes within the drug development process.

CONCLUSION

Coordination chemistry has been of huge application within medical chemistry especially after the synthesis of cis-platin. This led to the investigation of other transition elements and their effect on some of the leading diseases in the world. This includes diseases associated with microbes such as bacteria and fungi. Furthermore, diseases with sophisticated action mechanisms within the body such as cancer and diabetes mellitus also can be treated using drugs synthesized through applications of coordination chemistry. Metal-based antibacterial complexes include metal centers such as silver, zinc, copper and iron. Those which have antifungal action include zinc, silver, and manganese. Elements such as gold, platinum and ruthenium have been successfully tested for anticancer activity. Lastly, antidiabetic complexes include vanadium, zinc and cobalt. This review helps deepen understanding of the various mechanisms of the above metals that have therapeutic effects. These complexes have generic action mechanisms such as generation of reactive oxygen species, disruption of cell membrane and disruption of the DNA molecule.

Coordination chemistry has helped improve the efficiency of drugs due to its ability to help the active ingredient remains kinetically stable and arrive at the target area with little modifications. Although these complexes improve efficiency, they still have some level of toxicity which delays their approval within the drug development process. Therefore, it is not common to have a patient prescribed a transition metal-based drug. This calls for extensive research on proposed complexes or other new complexes which will have less toxicity and thus produce fewer side effects to the patient. This review does provide advancements for the medical chemistry and pharmaceutical industry by identifying key research gaps. These gaps include the need for extensive research on other transition elements and their potential, it also includes the need to use environmentally friendly preparation techniques. Addressing this will help develop more effective drugs which also help keep the planet safe.

Lastly, this literature review offers knowledge which is already common on coordination chemistry and its application through medical chemistry. Additionally, this review offers ways for future research and development in drug synthesis using transition metals. It highlights the most promising applications and offers areas which need further investigation and safer preparation methods. This can be used as a foundational source of information by researchers and medical personnel who are aiming to improve medical science and patient care using extensive applications of coordination compounds.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Ouellette, R.J. and J.D. Rawn, 17 - Organometallic Chemistry of Transition Metal Elements and Introduction to Retrosynthesis, in Organic Chem. Study Guide, R.J. Ouellette and J.D. Rawn, Editors. **2015**, Elsevier: Boston. 299-311.
2. Ouellette, R.J. and J.D. Rawn, 18 - Organometallic Chemistry of Transition Metal Elements and Introduction to Retrosynthesis, in Organic Chemistry (Second Edition), R.J. Ouellette and J.D. Rawn, Editors., **2018**, Academic Press. p. 537-559.
3. Aziz, K.N., K.M. Ahmed, R.A. Omer, A.F. Qader, and E.I. Abdulkareem, A review of coordination compounds: structure, stability, and biological significance. Reviews in Inorganic Chemistry., **2024**.

4. Kumar Singh, V.; V. Kumar Singh, A. Mishra, Varsha, A. Abha Singh, G. Prasad, and A. Kumar Singh, Recent advancements in coordination compounds and their potential clinical application in the management of diseases: An up-to-date review., *Polyhedron.,* **2023**, *241*, 116485.
5. Deore, A., J. Dhumane, R. Wagh, and R. Sonawane, The Stages of Drug Discovery and Development Process., *Asian Journal of Pharmaceutical Research and Development*., **2019**, *7*, 62-67.
6. Singh, N.; P. Vayer, S. Tanwar, J.-L. Poyet, K. Tsaioun, and B. Villoutreix, Drug discovery and development: introduction to the general public and patient groups., *Frontiers in Drug Discovery*., **2023**, *3*.
7. Lewnard, J. and A. Reingold, Emerging Challenges and Opportunities in Infectious Disease Epidemiology., *American Journal of Epidemiology*., **2019**, *188*, 873-882.
8. Cignarelli, A.; V.A. Genchi.; I. Caruso.; A. Natalicchio.; S. Perrini.; L. Laviola.; and F. Giorgino.; Diabetes and cancer: Pathophysiological fundamentals of a 'dangerous affair'., *Diabetes Research and Clinical Practice*., **2018**, *143*, 378-388.
9. Agrawal, P.; V. Kushwaha.; A. Das.; A. Sahu.; H. Vekaria, and S. Siddiqui, IATROGENESIS: AN OVERVIEW. *World Journal of Pharmaceutical Research*., **2023**, *12*, 222-231.
10. Ma, Z. and B. Moulton, Recent advances of discrete coordination complexes and coordination polymers in drug delivery., *Coordination Chemistry Reviews*., **2011**. *255*(15), 1623-1641.
11. Karges, J.; R.W. Stokes, and S.M. Cohen, Metal complexes for therapeutic applications., *Trends in Chemistry*., **2021**, *3*(7), 523-534.
12. Claudel, M., J. Schwarte, and K. Fromm, *New Antimicrobial Strategies Based on Metal Complexes. Chemistry*., **2020**, *2*, 849-899.
13. Sharma, B.; S. Sh, R. Rattan.; M. Fatima.; M. Goel.; M. Bhat.; S. Dutta, R. Rajan, and M. Sharma, Antimicrobial Agents Based on Metal Complexes: Present Situation and Future Prospects., *International Journal of Biomaterials*., **2022**. *2022*, 1-21.
14. Savithramma, N.; M. Rao.; K. Rukmini.; and P. Devi, Antimicrobial activity of Silver Nanoparticles synthesized by using Medicinal Plants., *International Journal of ChemTech Research*., **2011**, *3*.
15. Youngs, W.J.; A.R. Knapp.; P.O. Wagers, and C.A. Tessier, Nanoparticle encapsulated silver carbene complexes and their antimicrobial and anticancer properties: *A perspective. Dalton Transactions*., **2012**, *41*(2), 327-336.
16. Stankoviþ M.; J. Kljun, N.L. Stevanovi, J. Lazic, S. Skaro Bogojevic.; S. Vojnovic.; M. Zlatar.; J. Nikodinovic-Runic.; I. Turel, M.I. Djuran, and B.Đ. Gliši, Silver(i) complexes containing antifungal azoles: significant improvement of the anti-Candida potential of the azole drug after its coordination to the silver(i) ion., *Dalton Transactions*., **2024**, *53*(5), 2218-2230.
17. Rozhin, A.; S. Batasheva.; L. Iskuzhina.; M. Gomzikova, and M. Kryuchkova, Antimicrobial and Antifungal Action of Biogenic Silver Nanoparticles in Combination with Antibiotics and Fungicides Against Opportunistic Bacteria and Yeast., *International Journal of Molecular Sciences*., **2024**, *25*(23), 12494.
18. Al-Fartusie, F. and S. Mohssan, Essential Trace Elements and Their Vital Roles in Human Body., *Indian Journal of Advances in Chemical Science*., **2017**, *5*, 127-136.
19. Nandanwar, S.K. and H.J. Kim, Anticancer and Antibacterial Activity of Transition Metal Complexes., *Chemistry Select*., **2019**, *4*(5), 1706-1721.
20. Claudel, M.; J.V. Schwarte, and K.M. Fromm New Antimicrobial Strategies Based on Metal Complexes., *Chemistry*., **2020**, *2*, 849-899 DOI: 10.3390/chemistry2040056.
21. Biersack, B., Special Issue "Antifungal Drug Discovery: Progresses, Challenges, Opportunities". *International Journal of Molecular Sciences*., **2025**, *26*(5), 2065.
22. Ngece, K.; V. Khwaza, A.M. Paca, and B.A. Aderibigbe The Antimicrobial Efficacy of Copper Complexes: A Review. Antibiotics, **2025**, 14, DOI: 10.3390/antibiotics14050516.
23. Raducka, A.; M. Wiþtkowski.; I. Korona-Głowniak, B. Kapro.; T. Plech.; M. Szczesio.; K. Gobis.; M.I. Szynkowska-Jóþwik, and A. Czylkowska, Zinc Coordination Compounds with Benzimidazole Derivatives: Synthesis, Structure, Antimicrobial Activity and Potential Anticancer Application., *International Journal of Molecular Sciences*., **2022**, *23*(12), 6595.

24. Abu Ali, H.; S. Omar.; M. Darawsheh, and H. Fares, Synthesis, characterization and antimicrobial activity of zinc(II) ibuprofen complexes with nitrogen-based ligands., *J. of Coordination Chemistry*., **2016**, *69*, 1-28.
25. Lopez Venditti, E.D.; Karina F. Crespo Andrada, P.S. Bustos, M. Maldonado Torales, I. Manrrique Hughes, M.G. Paraje, and N. Guiñazú, Antibacterial, antifungal, and antibiofilm activities of biogenic zinc nanoparticles against pathogenic microorganisms., *Frontiers in Cellular and Infection Microbiology*., **2025**, *15*, 2025.
26. Galaris, D., A. Barbouti, and K. Pantopoulos, Iron homeostasis and oxidative stress: An intimate relationship., *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*., **2019**, *1866*(12), 118535.
27. Tarallo, M.B.; C. Urquiola, A. Monge, B.P. Costa, R.R. Ribeiro, A.J. Costa-Filho, R.C. Mercader, F.R. Pavan, C.Q.F. Leite, M.H. Torre, and D. Gambino, Design of novel iron compounds as potential therapeutic agents against tuberculosis., *Journal of Inorganic Biochemistry*., **2010**, *104*(11), 1164-1170.
28. Pandeya, S.N.; D. Sriram.; G. Nath, and E. De Clercq, Synthesis, antibacterial, antifungal and anti-HIV activities of norfloxacin Mannich bases., *European Journal of Medicinal Chemistry*., **2000**, *35*(2), 249-255.
29. Karegoudar, P.; D.J. Prasad, M. Ashok, M. Mahalinga, B. Poojary, and B.S. Holla, Synthesis, antimicrobial and anti-inflammatory activities of some 1,2,4-triazolo[3,4-b][1,3,4] thiadiazoles and 1,2,4-triazolo[3,4-b][1,3,4] thiadiazines bearing trichlorophenyl moiety., *European Journal of Medicinal Chemistry*., **2008**, *43*(4), 808-815.
30. Sheta, S.M.; S.R. Salem, and S.M. El-Sheikh, A novel Iron(III)-based MOF: Synthesis, characterization, biological, and antimicrobial activity study., *Journal of Materials Research*., **2022**, *37*(14), 2356-2367.
31. Gerwien, F.; V. Skrahina.; L. Kasper.; B. Hube.; and S. Brunke, Metals in fungal virulence., *FEMS Microbiology Reviews*., **2017**, *42*(1).
32. Ali, B. and M.A. Iqbal, Coordination Complexes of Manganese and Their Biomedical Applications., *Chemistry Select.*, **2017**, *2*, 1586-1604.
33. Scaccaglia, M.; M.P. Birbaumer.; S. Pinelli.; G. Pelosi, and A. Frei, Discovery of antibacterial manganese(i) tricarbonyl complexes through combinatorial chemistry., *Chemical Science*., **2024**, *15*(11), 3907-3919.
34. Wang, J.; Z.-M. Zhang.; C. Wang.; W. Shi.; M.-X. Li, and G.-P. Zu, Synthesis, characterization, antioxidant, and biological activity of manganese (II) complexes based on 2-acetylpyrazine thiosemicarbazones., *Transition Metal Chemistry*., **2025**, *50*(4)., 529-538.
35. Wu, Z.; F. Xia, and R. Lin, Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: a systematic analysis for the GBD 2021., *J. of Hematology & Oncology*., **2024**. *17*(1), 119.
36. Benedek, T.G., The history of gold therapy for tuberculosis., *J. of the History of Medicine and Allied Sciences*., **2004**, *59*, 50-89.
37. Todaria, M.; D. Maity, and R. Awasthi, Biogenic metallic nanoparticles as game-changers in targeted cancer therapy: recent innovations and prospects., *Future Journal of Pharmaceutical Sciences*., **2024**, *10*(1), 25.
38. Siddique, S. and J.C.L. Chow Gold Nanoparticles for Drug Delivery and Cancer Therapy., *Applied Sciences*., **2020**, *10*,DOI: 10.3390/app10113824.
39. Trudu, F.; F. Amato.; P. VaβHara.; T. Pivetta.; E.M. Peña-Méndez, and J. Havel,Coordination compounds in cancer: Past, present and perspectives., *Journal of Applied Biomedicine*., **2015**, *13*(2), 79-103.
40. Qian, D.; D. Zha.; Y. Sang.; J. Tao, and Y. Cheng, Moringa oleifera mediated green synthesis of gold nanoparticles and their anti-cancer activity against A549 cell line of lung cancer through ROS/ mitochondrial damage., *Frontiers in Chemistry*., **2025**, *13*.
41. Malik, M.A.; A.A. Hashmi.; A.S. Al-Bogami.; and M.Y. Wani.; Harnessing the power of gold: advancements in anticancer gold complexes and their functionalized nanoparticles., *Journal of Materials Chemistry* B., **2024**, *12*(3), 552-576.
42. Choudhary, S.; S.D. Kaur.; H. Gandhi.; D.B. Pemmaraju and D.N. Kapoor, An updated review on the potential of gold nanoparticles for cancer treatment and detection., *Gold Bulletin*., **2025**, *58*(1), 4.

43. Hato, S.V.; A. Khong.; I.J.M. de Vries.; and W.J. Lesterhuis, Molecular Pathways: The Immunogenic Effects of Platinum-Based Chemotherapeutics., *Clinical Cancer Research*., **2014**, *20*(11), 2831-2837.
44. Rimoldi, I.; V. Coccè.; G. Facchetti.; G. Alessandri.; A.T. Brini.; F. Sisto.; E. Parati.; L. Cavicchini.; G. Lucchini.; F. Petrella.; E. Ciusani, and A. Pessina, Uptake-release by MSCs of a cationic platinum(II) complex active *in vitro* on human malignant cancer cell lines., *Biomedicine & Pharmacotherapy*., **2018**, *108*, 111-118.
45. Czarnomysy, R.A.-O.; D.A.-O. Radomska.; O.K. Szewczyk.; P. Roszczenko and K. Bielawski, Platinum and Palladium Complexes as Promising Sources for Antitumor Treatments., LID-10.3390/ijms22158271 [doi] LID-8271. (1422-0067 (Electronic)).
46. Vaidya, S.P.; S. Gadre.; R.T. Kamisetti and M.A.-O. Patra.; Challenges and opportunities in the development of metal-based anticancer theranostic agents. LID-10.1042/BSR20212160 [doi] LID-BSR20212160. (1573-4935 (Electronic)).
47. Johnson, B.W.; M.W. Burgess.; V. Murray.; J.R. Aldrich-Wright and M.D. Temple, The interactions of novel mononuclear platinum-based complexes with DNA., *BMC Cancer*., **2018**, *18*(1), 1284.
48. Johnson, N.P.; J.-L. Butour.; G. Villani.; F.L. Wimmer.; M. Defais.; V. Pierson and V. Brabec. Metal Antitumor Compounds: The Mechanism of Action of Platinum Complexes. in Ruthenium and Other Non-Platinum Metal Complexes in Cancer Chemotherapy., **1989**. Berlin, Heidelberg: Springer Berlin Heidelberg.
49. Yang, J.; Y. Chen and H. Chao, A state-of-the-art view: G-quadruplex-targeting for platinum complexes' treatment of tumors., *RSC Chemical Biology*., **2025**, *6*(7), 1034-1047.
50. Ahmad, S.; Advances in anticancer applications of platinum(II) complexes of dithiocarbamates., *Medicinal Chemistry Research*., **2024**, *33*(7), 1133-1153.
51. Zeng, L.; P. Gupta.; Y. Chen.; E. Wang.; L. Ji.; H. Chao and Z.-S. Chen, The development of anticancer ruthenium(ii) complexes: from single molecule compounds to nanomaterials., *Chemical Society Reviews*., **2017**, *46*(19), 5771-5804.
52. Licona, C.; M.E. Spaety.; A. Capuozzo.; M. Ali.; R. Santamaria.; O. Armant.; F. Delalande.; A. Van Dorsselaer.; S. Cianferani.; J. Spencer.; M. Pfeffer.; G. Mellitzer and C. Gaiddon, A ruthenium anticancer compound interacts with histones and impacts differently on epigenetic and death pathways compared to cisplatin. (1949-2553 (Electronic)).
53. Zeng, L.; Y. Gupta P Fau-Chen.; E. Chen Y Fau-Wang.; L. Wang E Fau-Ji.; H. Ji L Fau-Chao.; Z.-S. Chao H Fau-Chen and Z. S. Chen, The development of anticancer ruthenium(ii) complexes: from single molecule compounds to nanomaterials. (1460-4744 (Electronic)).
54. Palmer, A.M.; R.B. Peña B Fau-Sears.; O. Sears Rb Fau-Chen.; M. Chen O Fau-El Ojaimi.; R.P. El Ojaimi M Fau-Thummel.; K. R. Thummel Rp Fau-Dunbar.; C. Dunbar Kr Fau-Turro and C. Turro.; Cytotoxicity of cyclometallated ruthenium complexes: the role of ligand exchange on the activity. (1364-503X (Print)).
55. Sun, Q.; Y. Li.; H. Shi.; Y. Wang.; J. Zhang.; and Q. Zhang.; Ruthenium Complexes as Promising Candidates against Lung Cancer. LID-10.3390/molecules26154389 [doi] LID - 4389. (1420-3049 (Electronic)).
56. Sava, G.; K. Clerici.; I. Capozzi.; M. Cocchietto.; R. Gagliardi.; E. Alessio.; G. Mestroni and A. Perbellini.; Reduction of lung metastasis by ImH[trans-RuCl4(DMSO)Im]: mechanism of the selective action investigated on mouse tumors., *Anti-Cancer Drugs*., **1999**, *10*(1).
57. Jayanthi, E.; S. Kalaiselvi.; V.V. Padma.; N.S.P. Bhuvanesh and N. Dharmaraj, Solvent assisted formation of ruthenium(iii) and ruthenium(ii) hydrazone complexes in one-pot with potential in vitro cytotoxicity and enhanced LDH, NO and ROS release., *Dalton Transactions*., **2016**, *45*(4), 1693-1707.
58. Bergamo, A.; B. Gava.; E. Alessio.; G. Mestroni.; B. Serli.; M. Cocchietto.; S. Zorzet.; and G. Sava., Ruthenium-based NAMI-A type complexes with *in vivo* selective metastasis reduction and *in vitro* invasion inhibition unrelated to cell cytotoxicity., *Int J Oncol.,* **2002**, *21*(6), 1331-1338.

59. D'Amato, A.; A. Mariconda.; D. Iacopetta.; J. Ceramella.; A. Catalano.; M.S. Sinicropi.; and P. Longo Complexes of Ruthenium(II) as Promising Dual-Active Agents against Cancer and Viral Infections., *Pharmaceuticals*., **2023**, *16*, DOI:10.3390/ph16121729.
60. Garrosa-Miró, Y.; L. Muñoz-Moreno.; G. D'Errico.; M. Tancredi.; M.J. Carmena.; M.F. Ottaviani.; P. Ortega and J. de la Mata, Ruthenium(ii) and copper(ii) polyamine complexes as promising antitumor agents: synthesis, characterization, and biological evaluation., *Dalton Transactions*., **2025**, *54*(18), 7506-7521.
61. Ganesan, S. and A. Sheela, Ruthenium and platinum-based anticancer metallotherapeutics from the perspectives of photodynamic therapy and bioimaging applications., *Chemical Papers*., **2024**, *78*(16), 8531-8561.
62. Azam, A.; M.A. Raza and S.H. Sumrra, Therapeutic Application of Zinc and Vanadium Complexes against Diabetes Mellitus a Coronary Disease: A Review. *Open Chemistry*., **2018**, *16*(1), 1153-1165.
63. Antar, S.A.; N.A. Ashour.; M. Sharaky.; M. Khattab.; N.A. Ashour.; R.T. Zaid.; E.J. Roh.; A. Elkamhawy, and A.A. Al-Karmalawy, Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments., *Biomedicine & Pharmacotherapy*., **2023**, *168*, 115734.
64. Banday, M.Z.; A.S. Sameer and S. Nissar., Pathophysiology of diabetes: An overview. (2231-0770 (Print)).
65. Amaral, L.M.P.F.; T. Moniz.; A.M.N. Silva.; and M. Rangel Vanadium Compounds with Antidiabetic Potential., *International Journal of Molecular Sciences*., **2023**, *24*, DOI: 10.3390/ijms242115675.
66. Winter, P.; A. Al-Qatati., A. Wolf-Ringwall, S. Schoeberl, P. Chatterjee, G. Barisas, D. Roess, and D. Crans, The anti-diabetic bis(maltolato)oxovanadium(IV) decreases lipid order while increasing insulin receptor localization in membrane microdomains., *Dalton transactions* (Cambridge, England: 2003)., **2012**, *41*, 6419-30.
67. Delgado-Rangel, L.H.; V. Reyes-Márquez.; M.E. Moreno-Narváez.; A. Aragón-Muriel.; J.R. Parra-Unda.; J.A. Cruz-Navarro.; M.A. Martínez-Torres.; H. Valdés and D. Morales-Morales, Biological activity of vanadium pincer complexes., *New Journal of Chemistry*., **2025**, *49*(9), 3442-3455.
68. Morales-Morales, D.; L. Delgado-Rangel.; V. Reyes.; M. Moreno.; A. Aragón-Muriel.; J. Unda.; J.A. Cruz-Navarro.; M. Martínez-Torres, and H. Valdés, Biological Activity of Vanadium Pincer Complexes., *New Journal of Chemistry*., **2024**. 2025.
69. Patel, N.; A.K. Prajapati.; R.N. Jadeja.; R.N. Patel.; S.K. Patel.; V.K. Gupta.; I.P. Tripathi.; and N. Dwivedi, Model investigations for vanadium-protein interactions: Synthesis, characterization and antidiabetic properties., *Inorganica Chimica Acta*., **2019**, *493*, 20-28.
70. Sanna, D.; A. Fadda.; M. Casula.; G. Palomba.; M.C. Sini.; M. Colombino.; C. Rozzo.; G. Palmieri.; C. Gallo.; D. Carbone.; L. Siracusa.; L. Pulvirenti and V. Ugone., Antidiabetic potential of vanadium complexes combined with olive leaf extracts: a viable approach to reduce metal toxicity., *BioMetals*., **2025**, *38*(2), 683-698.
71. Norouzi, S.; J. Adulcikas.; S.S. Sohal and S. Myers., Zinc stimulates glucose oxidation and glycemic control by modulating the insulin signaling pathway in human and mouse skeletal muscle cell lines., *PLOS ONE*., **2018**, *13*(1), e0191727.
72. Ranasinghe, P.; S. Pigera.; P. Galappatthy.; P. Katulanda and G.R. Constantine., Zinc and diabetes mellitus: understanding molecular mechanisms and clinical implications., *DARU J. of Pharmaceutical Sci.,* **2015**, *23*(1), 44.
73. Kawase, M.; N. Kagaya.; S. Akamatsu.; A. Kamiyoshi.; S.-i. Muto, Y.-i. Tagawa, and K. Yagi, Liver protection by bis(maltolato)zinc(II) complex., *Experimental animals*., **2004**, *53*, (1), 1-9.
74. Lihm, H.-S.; J. Cha.; J. Seo.; J. Park.; J. Lee.; H. Lee.; K.-S. Bae.; W. Kim and Y.-R. Yoon., Targeted Plasma Metabolite Profiling of Metformin in Healthy Korean Volunteers., *J. of Korean Society for Clinical Pharmacology and Therapeutics*., **2012**, *20*, 175.

75. Saito, R.; Y. Naito.; Y. Yoshikawa.; H. Yasui.; S. Kikkawa.; H. Ju.; R. Ohba.; T. Miyamoto.; S. Sano.; K. Maeda.; M. Tamura and I. Azumaya, Synthesis, crystal structure, and insulin-mimetic activity of zinc(ii) complexes with 4-alkyl- and 4,5-dialkyl-3-hydroxythiazole-2(3H)-thiones as a new class of hypoglycemic agent candidates., *New Journal of Chemistry*., **2025**, *49*(4): p. 1145-1158.
76. Ahmad, R.; R. Shaju.; A. Atfi and M.S. Razzaque Zinc and Diabetes: A Connection between Micronutrient and Metabolism., *Cells*., **2024**, *13*, DOI: 10.3390/cells13161359.
77. Ojo, O.; D. Fatokun.; I. Ejidike.; R. Awolope.; and S. Saheed.; Quercetin Zinc and Iron Metal Complexes Protect against Sodium Arsenite Intoxication in the Hepato-Renal System of Wistar Rats via the Oxidative Stress Pathway., *Journal of Toxicology*., **2022**. 2022, 1-10.
78. Maanvizhi, S.; T. Boppana.; C. Krishnan.; and A. Gnanamani.; Metal complexes in the management of diabetes mellitus: A new therapeutic strategy., *International Journal of Pharmacy and Pharmaceutical Sciences*., **2014**, *6*, 40-44.
79. Ma, Y.; W. Lin.; Y. Ruan.; H. Lu.; S. Fan.; D. Chen.; Y. Huang.; T. Zhang.; J. Pi and J.-F. Xu, Advances of Cobalt Nanomaterials as Anti-Infection Agents, Drug Carriers, and Immunomodulators for Potential Infectious Disease Treatment., *Pharmaceutics*., **2022**. *14*(11), 2351.
80. Kalinowska, M.; H. Lewandowska.; M. Pruszyβski.; G. Widerski.; E. Gołβbiewska.; K. Gryko.; J. Braun.; M. Borkowska.; M. Konieczna and W. Lewandowski, Co(II) Complex of Quercetin–Spectral, Anti-/Pro-Oxidant and Cytotoxic Activity in HaCaT Cell Lines., *Applied Sciences*., **2021**, *11*(19), 9244.
81. Umar, A.; M. Ashraf.; Aruba, S. Saeed.; M.Z. Tahir.; A. Ullah.; M. Aslam.; M. Abbas.; M. Parveen.; M. Khan.; M. Khan and H. Ullah.,Therapeutic Potential of Silver and Cobalt Nanoparticles in Sleep Disorders, Mental Health and Diabetes., *Archives of Clinical Case Studies*., **2025**, *4*.
82. Özaydın, C.; A. Tombak.; M. Boga and T. Kılıçoβlu., optical, electrical and photoelectrical properties of quercetin-co(ii) complex/n-si organic-inorganic hybrid device., *Middle East Journal of Science*., **2015**, *1*, 15-27.
83. Crichton, R.R., Metal Toxicity – An Introduction, in Metal Chelation in Medicine, R.R. Crichton, R.J. Ward, and R.C. Hider, Editors. **2016**, The Royal Society of Chemistry. p. 0.
84. Baeksgaard, L. and J.B. Sørensen, Acute tumor lysis syndrome in solid tumors--a case report and review of the literature. (0344-5704 (Print)).
85. Ishwarya, R.; R. Rajaganesh.; M. Geetha.; G. Kalaiarasi.; N. Arul.; J. Tharani.; K. Kavithaa and D. Sangeetha., Microbial synthesis of zinc oxide nanoparticles and their potential biological application as an antimicrobial and anticancer agent., *Biocatalysis and Agricultural Biotechnology*., **2024**, *62*, 103417.
86. Nkemzi, A.Q.; K. Okaiyeto.; O. Oyenihi.; C.S. Opuwari.; O.E. Ekpo and O.O. Oguntibeju, Antidiabetic, anti-inflammatory, antioxidant, and cytotoxicity potentials of green-synthesized zinc oxide nanoparticles using the aqueous extract of Helichrysum cymosum., *3 Biotech*., **2024**, *14*(12), 291.
87. Akbar, N.; Z. Aslam.; R. Siddiqui.; M. Raza.; and N. Khan, Zinc oxide nanoparticles conjugated with clinically-approved medicines as potential antibacterial molecules., *AMB Express*., **2021**, *11*.
88. Morgan, S.; P. Grootendorst.; J. Lexchin.; C. Cunningham and D. Greyson, The cost of drug development: A systematic review., *Health Policy*., **2011**, *100*(1), 4-17.
89. Schlander, M.A.-O.; K.A.-O. Hernandez-Villafuerte.; C.A.-O. Cheng.; J.A.-O. Mestre-Ferrandiz and M.A.-O.X. Baumann, How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. (1179-2027 (Electronic)).
90. Carvalho, F.P., Mining industry and sustainable development: time for change., *Food and Energy Security*., **2017**, *6*(2), 61-77.
91. Curry, J.A.; M.J.L. Ismay and G.J. Jameson, Mine operating costs and the potential impacts of energy and grinding., *Minerals Engineering*., **2014**, *56*, 70-80.
92. Haldar, S.K., Chapter 13 - Mineral Processing, in Mineral Exploration (Second Edition), S.K. Haldar, Editor. **2018**, Elsevier. p. 259-290.
93. Resnik, D.B., Postmarketing Research and Surveillance: Issues and Challenges. (1088-2111 (Print)).

94. Yaseen, G.; M. Ahmad.; M. Zafar.; A. Akram.; S. Sultana.; O. Kilic and G.D. Sonmez, Chapter 10 - Current status of solvents used in the pharmaceutical industry, in Green Sustainable Process for Chemical and Environmental Engineering and Science, Inamuddin., Editors. **2021**, Elsevier, 195-219.
95. Singh, O. and V.K. Singh, Chapter 20-The epitome of toxic dichloromethane (methylene chloride): An approach to understand hazards and safety, in Hazardous Chemicals, M. Chawla, J. Singh, and R.D. Kaushik, Editors. **2025**, Academic Press. 305-313.
96. Schlosser, P.M.; C.F. Bale As Fau-Gibbons, A. Gibbons Cf Fau - Wilkins, G.S. Wilkins A Fau-Cooper, and G.S. Cooper, Human health effects of dichloromethane: key findings and scientific issues. (1552-9924 (Electronic)).
97. Hagenaars, R.H.; R. Heijungs.; A. de Koning.; A. Tukker and R. Wang, The greenhouse gas emissions of pharmaceutical consumption and production: an input–output analysis over time and across global supply chains., *The Lancet Planetary Health*., **2025**. *9*(3), e196-e206.
98. Mishra, M.; M. Sharma.; R. Dubey.; P. Kumari.; V. Ranjan and J. Pandey, Green synthesis interventions of pharmaceutical industries for sustainable development., *Current Research in Green and Sustainable Chemistry*., **2021**, *4*, 100174.
99. Kumaravel, S.; P. Thiruvengetam and S. Kundu.; Chapter 6-Biosolvents as green solvents in the pharmaceutical industry, in Green Sustainable Process for Chemical and Environmental Engineering and Science, Inamuddin, Editors., **2021**, Elsevier, 105-149.
100. Becker, J.; C. Manske and S. Randl, Green chemistry and sustainability metrics in the pharmaceutical manufacturing sector., *Current Opinion in Green and Sustainable Chemistry*., **2022**, *33*, 100562.
101. Shahiwala, A.; Advancing drug delivery research: sustainable strategies for innovation and translation., *Drug Delivery and Translational Research*., **2025**.
102. Bhat, S. A.; G. Cui.; F. Ameen.; F. Li and S. Kumar, Chapter 8-Bioleaching: urban mining of E-waste and its future implications, in Global E-Waste Management Strategies and Future Implications, S. Arya and S. Kumar, Editors. **2023**, Elsevier. 143-151.
103. Johnson, D.B., Biomining-biotechnologies for extracting and recovering metals from ores and waste materials., *Current Opinion in Biotechnology*., **2014**, *30*, 24-31.
104. Ansari, S. and S. Fatima, 14-Prevention of liver problems from adverse chemical agents by healthy nutrition and Unani dietotherapy, in Phytochemistry, the Military and Health, A.G. Mtewa and C. Egbuna, Editors. **2021**, Elsevier. 257-273.
105. Serafini, M.; S. Cargnin, A.A.-O. Massarotti, T.A.-O. Pirali, and A.A.-O. Genazzani, Essential Medicinal Chemistry of Essential Medicines. (1520-4804 (Electronic)).
106. Egorova, K.S. and V.P. Ananikov, Toxicity of Metal Compounds: Knowledge and Myths., *Organometallics*., **2017**, *36*(21), 4071-4090.