Ind. J. Pharm. Edu. Res., 2025; 59(1s):s16-s24.
https://www.ijper.org

Review Article

Bio-Conjugated Metallic Complexes in Drug Design

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ABSTRACT

Background: This comprehensive review highlights the importance of bio-conjugated metallic complexes in drug design, particularly in the field of metallo-pharmaceutical science. The review emphasizes the need for biological relevance and the coordination of biomolecules or modified bio-compounds with metallic systems to maximize drug action and minimize toxicity. **Materials and Methods:** The objective of this review is to discuss various diseases, which exemplify the potential of bio-conjugated metallic complexes as a promising approach for drug design. **Results:** Utilizing physiologically active ligands in metal complexes has demonstrated improved antioxidant, antiviral, antitubercular and antitumor effects. **Conclusion:** Bio conjugated systems have become a viable method for creating molecules with several uses that are good for human health. The development of metal-based imaging agents and drug delivery systems has increased due to the conjugation of metals with biologically active compounds.

Keywords: Bio-conjugation, Metallic complexes, Drug design, Metallo-pharmaceutical science, Antioxidants, Chelate.

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Received: 22-09-2023;
Revised: 24-04-2024;
Accepted: 19-10-2024.

INTRODUCTION

The design of stable metal-based contrast agents for imaging and therapy has been the focus of extensive research in recent years.[1,2] One promising approach is to use chelating ligands that can form stable complexes with metal ions. These ligands are often tailored to bind specifically to the target biomolecule, such as an antibody, to enhance specificity and reduce off-target effects.[3] Chelating ligands; other strategies have also been explored, including encapsulation of the metal ion in nanoparticles or micelles, or incorporation of the metal ion into the structure of the biomolecule itself. Metals have a vital role in medicine, not only as contrast agents for diagnostic and therapeutic purposes but also as essential cofactors in many enzymes, known as metalloproteins.[4] These metalloproteins play a crucial role in various biological processes, such as metabolism, respiration and DNA replication.[5] The imbalance of metals in the body can lead to diseases, such as hemochromatosis and Wilson's disease, which require interventional and natural methods to restore equilibrium.[6]

The catalytic and structural properties of metal ions make them essential in many biological processes and certain metal ions in specific oxidation states are required for specific functions (Table 1). For example, iron is a critical component of heme, which is essential for oxygen transport in the blood.[7] Whereas, copper is necessary for electron transfer in cytochrome c oxidase, a crucial element in the respiratory series.[8] The role in enzymes, metals similarly show an essential protagonist in immune function, acting as signaling molecules and regulating inflammatory responses. Zinc, for example, is essential for the function of T-cells and NK-cells, while selenium plays a part in immune response to bacterial and viral infections.[9] The importance of metals in biological processes is vast and varied, ranging from the structural and catalytic properties of metalloproteins to the regulation of immune function. Further research in this field will undoubtedly reveal new insights into the character of metals in well-being of humanity and illness/disorders, which could lead to the development of novel therapies targeting metal-based pathways.

Bioinorganic chemistry plays a vital act in the expansion of metal-containing therapeutics, which has become a multi-billion-dollar industry in recent years. One of the focuses of this field; is the projection and synthesis of metal coordinates that can mimic the functional properties of natural metalloproteins. Metal ions, when coordinated with macromolecular ligands, can exhibit unique properties that are useful in medicinal chemistry.[10]

One area of interest in bioinorganic chemistry is the development of metal-based compounds that can mimic the action of insulin. Sodium vanadate and Bismaltolatooxovanadium (IV) complexes (BMOV) are two such compounds that have shown promising results in lowering blood sugar levels in diabetic patients. These metal-based compounds act by mimicking the action of insulin and enhancing glucose uptake by the body's cells.[11]

DOI: 10.5530/ijper.20255296

Gold and silver-based compounds are also being investigated for their potential in stabilizing blood glucose levels in diabetes patients.[12] These metal-based compounds work by binding to glucose molecules and enhancing their uptake by the cells. The bioinorganic chemistry is a rapidly growing field that has made significant contributions to the development of metal-containing therapeutics. Metal-based compounds, such as those that mimic the action of insulin, offer promising treatments for diabetes and other diseases. Further research in this growing area will undoubtedly lead to the expansion of novel metal-based therapies with enhanced efficacy and reduced side effects.[13]

Diabetes is a prolonged metabolic ailment that affects billions of individuals worldwide. Insulin injections and oral hypoglycemic drugs are the two main categories of drugs used to manage diabetes. While insulin injections are typically reserved for serious cases, oral hypoglycemic medications are generally appropriate for grownup patients.[14]

There are many types of oral hypoglycemic drugs existing in the marketplace, including sulphonylureas, biguanides and alpha-glucosidase inhibitors.[15] Sulphonylureas are medications that stimulate the pancreas to produce more insulin, helping to lessen blood glucose levels. They may be a source increase in weight, hypoglycemia, allergic responses and therefore contraindicated in gestation, lactation and Type 1 DM. Sulphonylureas work by disturbing the pancreatic β-cells and stimulating the crusade of insulin-containing secretory granules to the cell exterior and into circulatory system.[16]

Biguanides such as metformin, on the other hand, prevent the liver from producing glucose, thereby improving the body's response to insulin. Although they cause momentary side effects such as nausea, diarrhea, appetite loss and a metallic taste, biguanides are generally well tolerated. They are contraindicated in patients with nephro or hepatic disorders and heart problems. Another type of oral hypoglycemic drug is the alpha-glucosidase inhibitor (acarbose).[17] this medication acts by slowing down absorption of carbohydrates in the small intestine, thereby reducing the rise in blood sugar levels post meals. They may be reason behind side effects such as diarrhea, gas, constipation, or stomach pain. Despite the availability of these medications, the hunt for more smart and competent antihyperglycemic or hypoglycemic agents continues. One area of investigation focuses on clinically permitted use of metal-comprising molecules to identify newer medicinal compounds from all through the periodic table to be cast-off anti-hyperglycemic as well as antioxidant tackles.[18,19]

Bio-mineralization

Elemental medicine has emerged as a rapidly developing field focused on the development of novel therapeutic and diagnostic metal complexes. Researchers have made significant improvements in the biotransformation of metal complexes and aiming for various diseases. Platinum therapeutics, gold anti-arthritic and bismuth antiulcer agents have been dynamic research targets for eras.[20] Studies have shown that iron and copper complexes can be more effective in cell destruction and inhibiting DNA synthesis than uncompelled organic moieties.[21]

The arena of inorganic chemistry in medical line can be broadly categorized in dual classes. The first involves moieties as drugs that aim metal ions in certain way, either free or protein-bound. The second involves metal-dependent drugs and imaging compounds, in which core metal ion plays a critical role in the mechanism of action.[22] Researchers are also interested in molecules of metals with previously recognized organic medicines, such as aspirin, paracetamol and metformin. It has been observed that the biological significance of these compounds upsurges on associating with the particular ligands, resulting in organic medicinal coordinates.[23]

Studies in this area has made substantial advancement in utilizing transition metal agents as agents to cure many human ailments, including carcinomas, lymphomas, infection control, anti-inflammatory, diabetes and neurological diseases.[24] Therefore, development of metal conjugates for medical applications has great potential to revolutionize the management of various disorders and improve patient outcomes. Cancer holds the second position behind high mortalities around the world. The findings on antitumor property of cisplatin initiated an exploration for other metal adducts with cytotoxic activities against malignancies. An immediate evidence concerning antitumor tendencies of the top ten active metals: As, Sb, Bi, Au, V, Fe, Rh, Ti, Ga and Pt have been at present updated. In spite of the effectiveness of cancer cure employing cisplatin, the usage is still restricted on account of critical adverse effects such as neuro-, hepato- and nephrotoxicity and through resistance phenomenon.[25] Gold (III)-dithiocarbamato conjugate has currently extended growing consideration as possible anticancer agents for the reason of their severe tumor cell growth inhibition actions, commonly accomplished by misusing non-cisplatin like MOA. The field of medicinal chemistry has seen significant progress in the advance of non-platinum dependent anticancer agents. Among these, Mo-based complexes have shown potential in curing diseases such as cancer and malignant. Ruthenium compounds have also emerged as promising drug candidates due to their lessened toxicity and ability to be abided *in vivo.* The different OS, MOA and ligand replacement kinetics of ruthenium molecules contribute an advantage above platinum-based complexes, providing a promising cytotoxic profile.[26]

Transition metals, such as ruthenium, also play an essential role as micronutrients and co-factors of different metalloenzymes in biological systems.[27] this additionally supports the validation behind synthesizing and evaluating novel transition metal-based complexes for their antitumor activities. The application of replaced organic ligands and their metal conjugates shows potential in bringing forth effective anticancer agents. Structural

modifications could afford these complexes improved strength beside a range of malignancies, along with little toxicity and enhanced solubility.[28]

Research in this area continues to progress, with a focus on developing metal complexes with novel ligands and evaluating the efficacy and toxicity of these compounds. The expansion of new metal-based drugs and imaging agents with specific targeting properties is also an active area of research. The application of metal complexes in medicinal chemistry has the potential to revolutionize cancer treatment and other diseases.[29]

Metal-Based Antioxidants

Antioxidants have expanded much consideration in recent ages for their possible health benefits due to their capacity to scavenge free radicals and stop oxidative damage to cells. Transition metal complexes have emerged as promising candidates for antioxidant therapy due to their unique chemical properties. Particular, Co (II), Ni (II), Cu (II) and Mn (II) conjugates have shown to possess antioxidant activity.[30]

Various methods have been developed to govern the antioxidant commotion of these complexes. *In vitro* studies grounded on biological oxidants, such as O_2•-, HO•, H_2O_2, ROO• and NO• radicals are commonly used to gauge the antioxidant property of metal complexes. On-biological testing methods, such as the scavenging of two, DPPH• assay and the foraging of ABTS assay, are also widely used. The TBARS and protein carbonyl assays seems to be employed to assess antioxidant activity.[31]

Recently, a novel electrochemical approach has been developed to appraise the antioxidant activity of metal complexes. This method depends on reaction with the stable radical 2, 2′-Diphenyl-1-Picrylhydrazyl (DPPH) censored through RDE method. Compared to traditional spectrophotometric assays, this electrochemical approach is advantageous as seems to be applicable to colored molecules and in a varied array of deliberations.[32]

Dementia Related Metallic Arrangements

Metal chelating agents have been examined for their budding capability to treat Alzheimer's Disease (AD) due to their ability to bind to metal ions such as copper and iron, which are involved in the development of beta-amyloid plaques in the brain. Quercetin, a natural flavonoid, has been studied as an antioxidant and metal chelator for its potential in treating AD.[33] Studies have shown that Ni(II) complex of 6-bromo-3-(3(4-chlorophenyl) acryloyl)-2H-chromen-2-one exhibits superior antioxidant activity compared to other metal complexes such as Cobalt (II), Copper (II) and Manganese (II).[34]

Metal adducts are found to possess higher free radical scavenging activity than their respective free ligands, making them potential therapeutic agents for diseases such as AD. Some metal complexes with antioxidant properties have also demonstrated significant larvicidal activity. The synthetic chemistry community has been focusing on developing bioactive compounds for anti-malignant, antioxidant and enzyme inhibition researches in *in vitro* and *in vivo* subjects.[35]

The growth of metal-based therapeutics has become an important area of research, as they offer the potential for targeted therapies with lower toxicity compared to traditional chemotherapy drugs. In particular, metal complexes with unique structures and properties have resulted promising outcomes in preclinical studies for the management of different cancers and other diseases.[36]

The Biomarkers

Biochemical alleyways are highly complex and dynamic and their depiction in diagrams and models requires simplification to some extent. However, the challenge for molecular and cell biologists is to recognize that the labels assigned to various proteins or molecules in these depictions do not reflect the full range of their interactions and functions in the cell. For example, labeling a protein as a GFP and assuming it will continue to function in the same way is a simplistic view. Scientists now understand that observing living organisms at the molecular level can perturb the precise things they are trying to study and efforts are being made to minimize these effects through innovative techniques

Table 1: Common amino acids with their nature.

Sl. No.	Amino acids	Amino acid type
1	Alanine	Nonpolar, aliphatic
2	Arginine	Polar, basic
3	Asparagine	Polar uncharged
4	Aspartic acid	Polar, acidic
5	Cysteine	Polar, uncharged
6	Glutamic acid	Polar, acidic
7	Glutamine	Polar, uncharged
8	Glycine	Nonpolar, aliphatic
9	Histidine	Polar, basic
10	Isoleucine	Nonpolar, aliphatic
11	Leucine	Nonpolar, aliphatic
12	Lysine	Polar, basic
13	Methionine	Nonpolar, aliphatic
14	Phenylalanine	Nonpolar, aromatic
15	Proline	Nonpolar, aliphatic
16	Serine	Polar, uncharged
17	Threonine	Polar, uncharged
18	Tryptophan	Nonpolar, aromatic
19	Tyrosine	Polar, aromatic
20	Valine	Nonpolar, aliphatic

and technologies.[37] Antidiabetic and antioxidant investigation, mounting biomarkers and treatment stratagems have both received significant attention. For instance, several studies have identified potential biomarkers for early detection and diagnosis of diabetes, including HbA_{1c}, FPG and OGTT. The use of natural antioxidants such as quercetin, resveratrol and curcumin (Figure 1) has gained interest as potential therapeutic agents for managing oxidative stress-related complications in diabetes.[38]

The current research focus is on the development of innovative strategies for targeting specific molecules involved in diabetes and antioxidant pathways (Figure 2). For instance, antagonists of DPP-4 and SGLT2 shown promising results in managing blood glucose levels and reducing the threat of cardiovascular complications in human subjects with diabetes.[39] Similarly, targeting specific molecules involved in antioxidant pathways, such as Nrf2 and HO-1 is being scrutinized as a potential therapeutic approach for reducing oxidative stress-related complications in diabetes.[40]

Diabetes and Bio-coupling

Metallopharmaceutical drugs have been studied as potential treatments for diabetes.[41] Thiazolidinediones (TZD) found as active anti-diabetic drugs that mend insulin response via stimulation of PPAR-γ and adipocyte-specific transcription factor. Recently, selective PPARγ modulators (sPPARγM) have been discovered that hold insulin-sensitizing response while minimizing side effects equated to traditional TZDs. *In vitro* assays using an amalgamation of docking, SPR-based interaction, luciferase reporter, etc., used to investigate binding mode, binding affinity and positive response of L312 to PPARγ.[42]

Pharmaceutical isoforms that have an anti-diabetic effect have been found to improve biochemical parameters, which is likely due to their high content of polyphenolic compounds. These compounds have been found to have beneficial properties on insulin sensitivity, glucose homeostasis and oxidative stress in preclinical and clinical studies.[43] Researchers have focused on identifying effective antihyperglycemic agents for the treatment of diabetes. Among them, metallic compounds such as vanadium complexes have shown promising results in STZ-induced diabetic rats. Vanadate and vanadyl forms of vanadium found to possess insulin-like effects in various cells, indicating their potential as antidiabetic agents. To improve the efficacy of antidiabetic drugs, current research is focused on exploring the basic aspects of diabetes, including the molecular categorization of insulin, its chemical basis and secretion, as well as the mode of action of hypoglycemic drugs associated with diabetes.[44]

In a comparative study of isoforms of bis (maltolato) oxovanadium (IV) (BMOV) having different metallic centers, it was found that BMOV, in an orally available formulation, is the most effective glucose- and lipid-lowering agent among all isoforms studied. This indicates that the meticulous selection of ligands and metals is crucial for formulating efficient antidiabetic compounds; the discovery of metallic compounds like vanadium complexes and the identification of effective antidiabetic agents like BMOV highlight the importance of ongoing research in the development of efficient treatments for diabetes. These findings may pave the way for the improvement of new and improved antidiabetic drugs. The bio conjugate chemistry of antihyperglycemic metallic complexes has offered promising outcomes in the quest for efficient antidiabetic agents. The usage of Cr (III)-amino acid complex contrary to nicotinamide-streptozotocin originated diabetic Wistar rats exposed that supplement Cr (III)-complex for 8 weeks lessened the blood sugar level in the array of 46.446-79.593%.[45] The V-(IV)-adenine adduct got announced as potential pharmacological exemplary for diabetic problems. It has been reported that a Zinc Metal-Organic Framework (ZMOF) with noticeable *in vivo* anti-diabetic activity and low *in vitro* cell toxicity was made utilizing 5-aminotetrazole and methyl-2-amino-4-isonicotinate anionic moiety.[46] In order to cure non-insulin dependent DM and turn out as an antioxidant, neodymium N, N-dimethylbiguanide hydrochloride complexes have been developed and their activity has been strongly influenced by the location of the functional group within each ligand. An important approach in the creation of ligands with advantageous features is the use of biogenic ligands.[47] when developing a potent anti-diabetic medication, the choice of ligands and metals should be carefully taken into account. These complexes' agonistic activity, affinity and interaction pattern with their targets is crucial to properly understanding the mechanism of action of these compounds.[48] Natural compounds including chromones, flavonoids and coumarins are gaining increased interest in the field of bio conjugate chemistry due to their potential medical applications. When complexed with metal ions, these compounds exhibit enhanced medical properties, making them suitable for the treatment of diseases like diabetes mellitus.[49] Recent research has focused on the regulation of Human Aldose Reductase (HAR) enzymatic activity, which has potential therapeutic applications in DM. Docking studies of HAR with dissimilar ligands, including embelin, copper-embelin complex, zinc-embelin complex, vilangin and quercetin (Figure 3) have been conducted to evaluate their putative binding sites and interaction energy. The study found that vilangin had the highest interaction energy (-48.94 kcal/mol) while metformin had the minimum interaction energy (19.52 kcal/mol) in comparison to many other scrutinized ligands, making them potential candidates for HAR inhibitory activity and the deterrence of DM-associated disorders.[50] These outcomes deliver new awareness into the prospective of natural compounds as antidiabetic agents and highlight the importance of bio conjugate chemical drug research in developing efficient antidiabetic agents.

Recent research has highlighted the significance of enantiomer's in the ligand-target interactions and biological activities of target compounds. In a study evaluating the antioxidant activity of

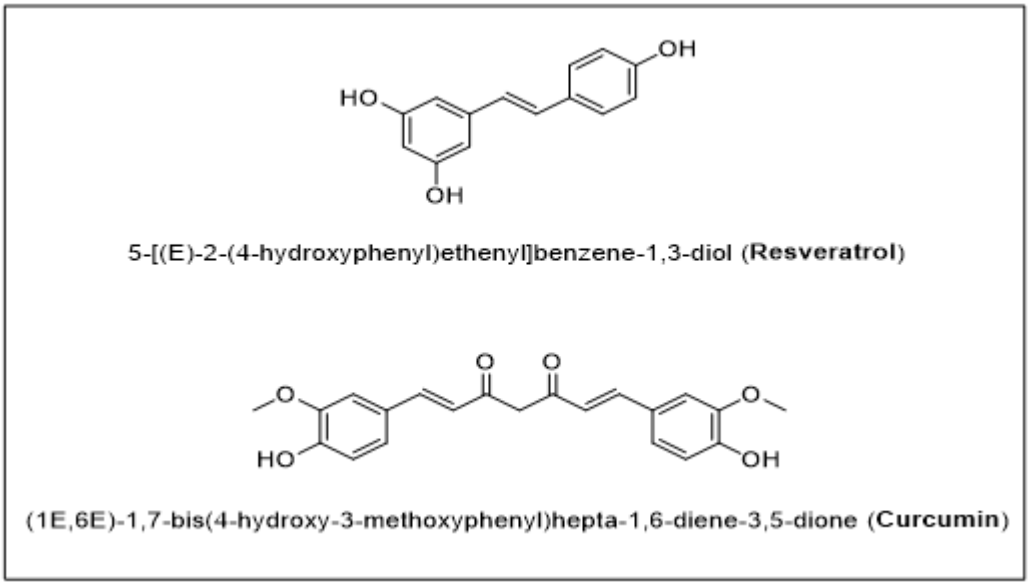

Figure 1: Chemical structure of resveratrol and curcumin.

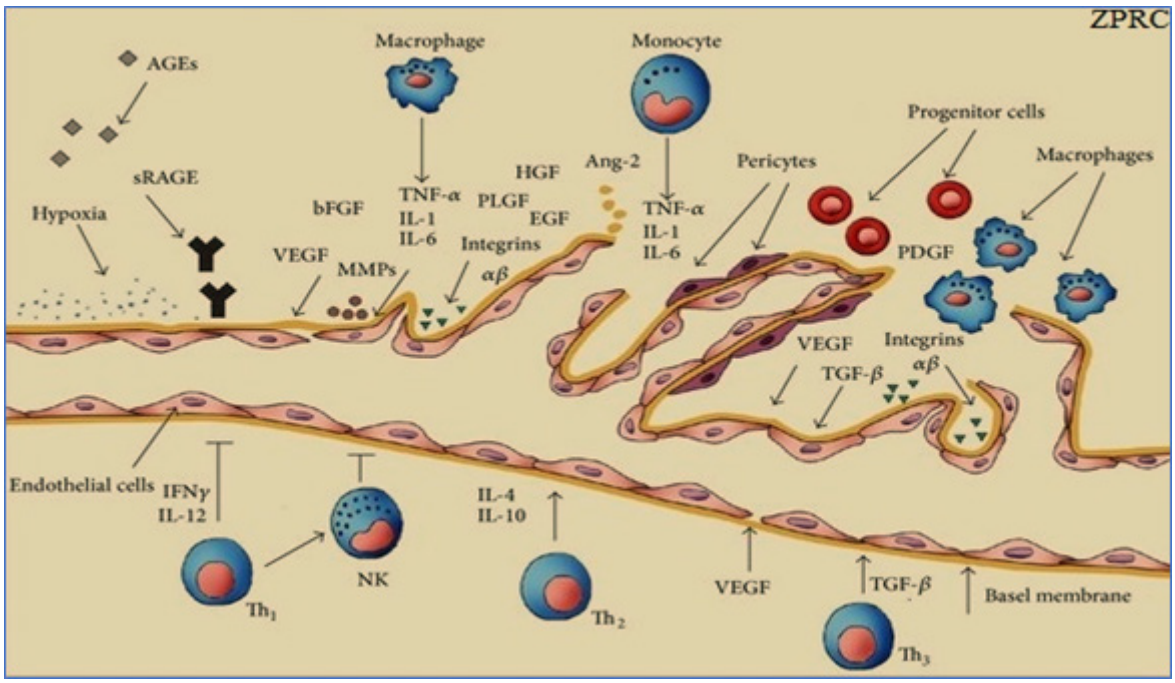

Figure 2: Biomarkers in biological system.

resveratrol using *in vitro* and *in vivo* methods, it was found that the biological activity of the compound is largely dependent on its enantiomeric form.[51] This emphasizes the need to consider the stereochemistry of target compounds when designing ligands for their targets.

Molecular modeling studies have also played a crucial role in understanding ligand-target interactions and their mode of action. By predicting the binding mode and affinity of a ligand with its target, molecular modeling provides valuable insights into the design of ligands with improved potency and selectivity. In particular, molecular docking has been extensively used to study ligand-protein interactions and its accuracy has been verified by experimental results.[52] Computer aided drug design such as molecular dynamics simulations and free energy calculations have also been employed to study the dynamics of ligand-target complexes and the free energy changes associated with their binding.[53]

Antioxidant Activity and Bio conjugation

Antioxidant studies are performed using various standard methods and it has been found that metal dyshomeostasis is allied

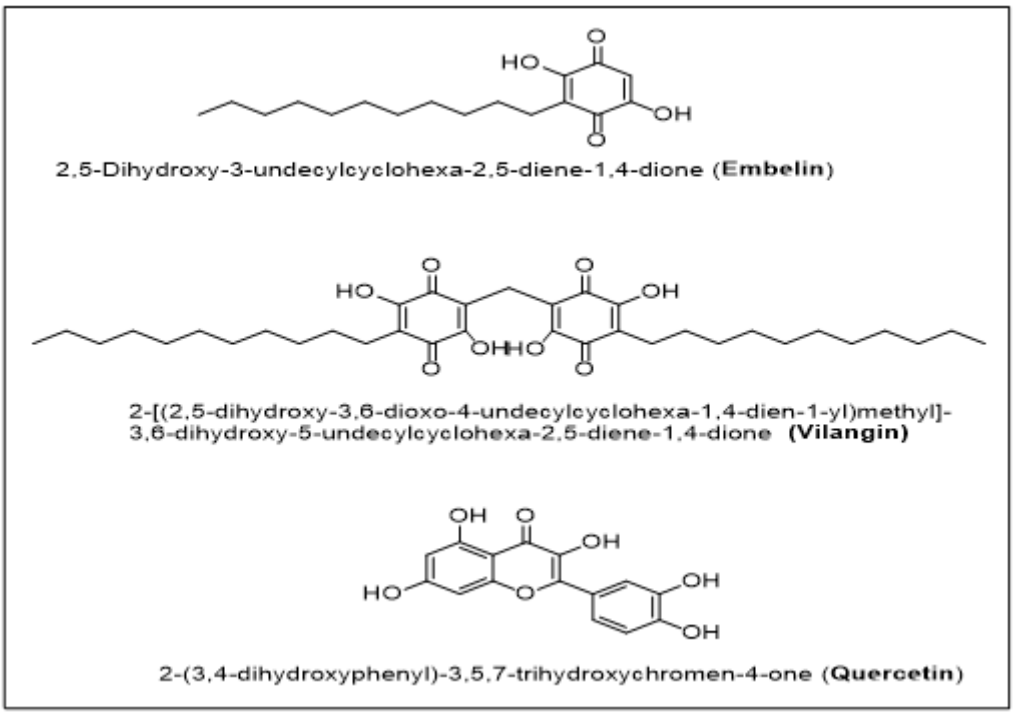

Figure 3: Chemical structure of Embelin, Vilangin and Quercetin,

with various ailments, including AD, Parkinson's and cancer. Latest reports suggested that certain metallic compounds of certain ligands might exhibit activity while others may be inactive in antioxidant activity tests using picryhydrazyl (DPPH).[54]

Polyphenols was recommended as competent antioxidant and anti-inflammatory contenders and their metallic complexes are projected to unveil boosted antioxidant action due to the malleable oxidation state of the metal center. Ni complexes of NSAID diflunisal (Hdifl) have been found to result in additive antioxidant effects of the respective ligand.[55] It was directed that ligand-receptor associations and cellular events are principally reliant on the enantiomerism of a receptor moiety, as observed in the case of resveratrol. Therefore, the choice of ligands and metals in designing antioxidant compounds should be done meticulously to obtain efficient results. Further investigations are needed to better comprehend the approach of action of these compounds and their potential therapeutic applications.

Antioxidant activity is an important characteristic of many compounds, as it has been linked to several health benefits, including decline in the possibility of chronic diseases such as cancer and cardiovascular diseases.[56] The use of metal complexes has gained attention in the development of compounds with enhanced antioxidant activity. One of the reasons for this is the flexibility of the oxidation state of metal centers, which allows them to participate in various redox reactions and potentially enhance the antioxidant action of the ligand.

Several studies have investigated the antioxidant activity of metal complexes of various ligands. For instance, the Cu (II) conjugate of bis (N-(3-methoxysalicylidene)-4-amino-phenyl) ether has been shown to exhibit superior antioxidant effectiveness against radicals of DPPH, O_2, -OH and ABTS compared to the ligand and the Mn (III) conjugate.[57] In another study, biotin-8-hydroxyquinoline conjugates and their metal conjugates with Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) were investigated for their potential application in oxidative stress and were found to exhibit varying degrees of antioxidant activity. Similarly, metallic amalgams of p-coumaric acid, 2-(3-amino-4, 6-dimethyl-1H-pyrazolo3, 4-bpyridin-1-yl) aceto-hydrazide and chromone Schiff base have also shown enhanced antioxidant activity compared to their respective ligands.[58]

It is important to note that the choice of ligand and metal should be carefully considered to articulate an effective antioxidant complex. Additionally, the method used to evaluate antioxidant activity can also affect the results obtained. Various standard methods, such as DPPH, ABTS, superoxide and hydroxyl radical scavenging methods, are commonly used to evaluate antioxidant activity.[59] Recent studies have shown that some metallic compounds of certain ligands may exhibit activity or inactivity depending on the method used. The ability of a complex to avoid ROS generation is another important aspect to consider in antioxidant studies. Ag complex of one, 10-phenanthroline has exposed fascinating behavior in this background. This complex has been shown to have potent antioxidant activity and exhibits a shielding effect contrary to hydrogen peroxide-induced oxidative stress in human fibroblast cells. Importantly, it does not generate ROS, which is a desirable property as ROS can cause oxidative damage to cells.[60]

Sugar and Urea Derivative Centered Complexes

Urea derivatives are a group of pharmacologically active ligands that have been extensively studied due to their biological properties, such as anti-tubercular and antiviral potential, as well as their activity against protozoa, smallpox and certain types of tumors.[61] Thiosemicarbazone is another class of ligands that has been widely studied for its chelating properties with diverse metal ions, including transition and non-transition elements.

The capability of sugars in seizing metal has gained attention in the conceivable growth of metal chelates for scientific application and prototypes for biologically essential molecules. Amino sugars can formulate Schiff base using salicylaldehyde, with some additional aromatic aldehydes, though limited information of transition metal complexes of synthesized molecules were established. Metal chelation has been proposed as a sensible therapeutic tactic for prohibiting Alzheimer's pathogenesis. In AD, amyloid plaques, which exist as bunches of peptides and metal ions, accumulate amid neurons inside brain. Augmenting the pursuing and efficiency of metal-ion chelates as representatives over sugar-appended ligands brings a latest tactic in progress of subsequent generation of metal chelators.

CONCLUSION

An integration of biomolecules and metallic systems has opened new avenues in the area of medicinal chemistry. The use of metal complexes of biologically active ligands has shown enhanced antioxidant, anti-tubercular, anti-viral and anti-tumor properties. Thiosemicarbazone has been extensively studied for their chelating properties with different metal ions. Moreover, the chelation of metals through amino sugars has shown promise as a therapeutic strategy for forbidding Alzheimer's disease pathogenesis.

Metallo-pharmaceuticals have been designed to mimic gasotransmitter pathways for potential therapeutic applications. Bio conjugated systems have emerged as a promising approach to developing multi-purposeful compounds with beneficial effects for human health. The conjugation of metals with biologically active molecules has raised the development of metal-based imaging agents and drug delivery systems. With further research, these bio-conjugated systems have the potential to develop highly effective and targeted compounds for various human health applications. The combination of biomolecules and metallic systems is a fruitful area for future exploration and development of novel therapeutic agents.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Nk-Cells: Natural Killer Cells; **DM:** Diabetes Mellitus; **$O_2^{\bullet-}$:** Superoxide Radical; **HO•:** Hydroxyl Radical; **$H_2O_2^{\bullet}$:** Hydrogen Peroxide Radical; **ROO•:** Peroxyl Radical; **NO•:** Nitric Oxide Radical; **DPPH:** 2, 2′-Diphenyl-1-Picrylhydrazyl; **ABTS:** 2, 2-Azinobis-(3-Ethylbenzothiazoline6-Sulphonate); **RDE:** Rotating Disk Electrode; **AD:** Alzheimer's Disease; **GFP:** Green Fluorescent Protein; **Hba1c:** Glycated Hemoglobin; **FPG:** Fasting Plasma Glucose; **OGTT:** Oral Glucose Tolerance Test; **Dpp-4:** Dipeptidyl Peptidase 4; **SGLT 2:** Sodium-Glucose Cotransporter 2; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **HO-1:** Heme Oxygenase-1; **TZD:** Thiazolidinediones; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor Gamma; **STZ:** Streptozotocin; **HAR:** Human Aldose Reductase; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **OS:** Oxidation State; **MOA:** Mechanism Of Action.

SUMMARY

Bioconjugation is a versatile technique used to attach various molecules, such as peptides, proteins, or ligands, to metallopharmaceuticals. Metallopharmaceuticals are drugs or therapeutic agents that contain metal ions as an integral part of their structure and function. These metal ions often play a crucial role in the therapeutic action of the drug. Bio-conjugated metallic complexes in drug design offer a versatile approach to enhance the therapeutic properties of metal-based drugs. Their ability to enable targeted drug delivery, improve imaging capabilities and facilitate combination therapies makes them valuable tools in modern pharmaceutical research and development.

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Cite this article: Patle D, Sengar NPS. Bio-Conjugated Metallic Complexes in Drug Design. Indian J of Pharmaceutical Education and Research. 2025;59(1s):s16-s24.