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Plant-Derived Metal Coordination Complexes for Synthesis Structural Characterization Biological Activities and Pharmaceutical Applications

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Abstract

Plant-derived bioactive compounds have attracted significant scientific attention as natural ligands for the synthesis of metal coordination complexes with enhanced biological and pharmaceutical properties. Numerous phytochemicals, including flavonoids, polyphenols, alkaloids, terpenoids, phenolic acids, coumarins, tannins, and glycosides, possess multiple donor atoms such as oxygen, nitrogen, and sulfur that readily coordinate with biologically important metal ions. The resulting coordination complexes often exhibit improved physicochemical stability, enhanced bioavailability, increased pharmacological efficacy, and reduced toxicity compared with their parent compounds. Metal ions including copper, zinc, iron, cobalt, nickel, manganese, ruthenium, silver, and vanadium have demonstrated remarkable synergistic interactions with plant-derived ligands, producing complexes with potent antimicrobial, antioxidant, anticancer, anti-inflammatory, antiviral, antidiabetic, and neuroprotective activities. Recent advances in green chemistry have facilitated environmentally friendly synthesis routes using plant extracts as reducing, stabilizing, and complexing agents, minimizing hazardous chemical usage while promoting sustainable pharmaceutical development. Sophisticated analytical techniques including UV–Visible spectroscopy, Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), mass spectrometry (MS), X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), and density functional theory (DFT) have substantially improved structural characterization of these complexes.

Keywords: *Plant-derived ligands, Bioinorganic chemistry, Medicinal chemistry, Pharmaceutical applications, Structural characterization, Biological activity.*

1. Introduction

Natural products have served as one of the most important sources of therapeutic agents throughout human history, contributing substantially to the discovery and development of modern pharmaceuticals. Plants produce a diverse array of secondary metabolites that possess remarkable structural diversity and biological activity. These naturally occurring compounds not only function as defense molecules against environmental stress and pathogens but also exhibit significant pharmacological properties valuable for human health. Recent advances in coordination chemistry have demonstrated that complexation of plant-derived molecules with transition metal ions can substantially improve their biological efficacy, chemical stability, solubility, and pharmacokinetic behavior [1]. Coordination chemistry investigates the interaction between metal ions and organic or inorganic ligands through coordinate covalent bonding. Many phytochemicals contain functional groups capable of donating electron pairs to metal ions, including hydroxyl, carbonyl, carboxyl, amino, thiol, and methoxy groups. These donor atoms enable the formation of stable coordination complexes with biologically essential metals such as copper, zinc, iron, manganese, cobalt, magnesium, calcium, and several transition metals. Metal coordination frequently modifies the electronic structure, redox potential, lipophilicity, and molecular geometry of plant-derived compounds, resulting in enhanced therapeutic performance.

Plant-derived coordination complexes have emerged as promising candidates in medicinal chemistry because they often demonstrate superior antimicrobial, antioxidant, anticancer, anti-inflammatory, antiviral, antiparasitic, antidiabetic, and neuroprotective activities compared with their corresponding free ligands. The synergistic interaction between metal ions and phytochemicals contributes to multiple mechanisms of biological action, including reactive oxygen species modulation, enzyme inhibition, DNA interaction, protein binding, apoptosis induction, and immune regulation [2]. Green chemistry principles have further accelerated research in this field by encouraging sustainable synthesis methods that minimize environmental pollution and hazardous chemical consumption.

Plant extracts rich in polyphenols, flavonoids, alkaloids, tannins, and reducing agents serve simultaneously as natural complexing agents, stabilizers, and reducing agents during coordination complex synthesis. These environmentally benign approaches align with global efforts toward sustainable pharmaceutical manufacturing and eco-friendly chemical processes. Recent developments in advanced spectroscopic, microscopic, thermal, and computational characterization techniques have significantly improved structural elucidation of coordination compounds [3]. These analytical advances facilitate precise determination of coordination geometry, metal-ligand interactions, electronic structure, crystal morphology, thermal stability, and biological behavior, thereby supporting rational drug design and pharmaceutical development.

2. Plant-Derived Phytochemicals as Natural Ligands

Plants synthesize thousands of structurally diverse secondary metabolites capable of coordinating with metal ions through various donor atoms. These naturally occurring ligands possess remarkable chemical versatility due to the presence of oxygen-, nitrogen-, sulfur-, and occasionally phosphorus-containing functional groups that participate in coordination bond formation. The diversity of phytochemical structures allows the synthesis of coordination complexes with varying geometries, coordination numbers, electronic configurations, and biological activities. Flavonoids represent one of the largest classes of naturally occurring polyphenolic compounds used as ligands in coordination chemistry [4]. Molecules such as quercetin, kaempferol, luteolin, rutin, catechin, apigenin, and hesperidin possess multiple hydroxyl and carbonyl groups capable of chelating transition metal ions. Complex formation generally occurs through adjacent hydroxyl groups or carbonyl-hydroxyl combinations, producing stable five- or six-membered chelate rings. Flavonoid-metal complexes frequently demonstrate enhanced antioxidant, antimicrobial, anticancer, and anti-inflammatory activities relative to the parent flavonoids.

Phenolic acids, including gallic acid, caffeic acid, ferulic acid, chlorogenic acid, and ellagic acid, constitute another important category of natural ligands. Their carboxyl and phenolic hydroxyl groups readily coordinate with divalent and trivalent metal ions, improving redox properties and biological effectiveness. Similarly, tannins exhibit exceptional metal-binding capacity owing to their numerous hydroxyl groups, enabling the formation of highly stable coordination complexes with iron, copper, aluminum, and other transition metals. Alkaloids represent nitrogen-containing natural compounds with strong coordination ability [5]. Molecules such as berberine, quinine, morphine, caffeine, nicotine, and colchicine contain heterocyclic nitrogen atoms capable of coordinating with various metal ions. Metal complexation frequently enhances antimicrobial activity, DNA binding affinity, enzyme inhibition, and anticancer potential.

Terpenoids, coumarins, lignans, glycosides, xanthones, anthraquinones, and sulfur-containing phytochemicals also contribute significantly to natural ligand chemistry. Their structural diversity provides numerous coordination possibilities, facilitating the design of multifunctional metal complexes for pharmaceutical applications. The selection of appropriate plant-derived ligands depends upon metal ion preference, coordination geometry, desired biological activity, and pharmaceutical objectives. The combination of naturally occurring ligands with biologically relevant metal ions has created a rapidly expanding research field bridging phytochemistry, coordination chemistry, pharmacology, and nanotechnology.

Table 1: Major Classes of Plant-Derived Ligands Used in Metal Coordination Chemistry

Phytochemical Class	Representative Compounds	Major Donor Groups	Common Coordinating Metals
Flavonoids	Quercetin, Kaempferol, Rutin	Hydroxyl, Carbonyl	Cu, Zn, Fe, Co
Phenolic Acids	Gallic acid, Caffeic acid	Hydroxyl, Carboxyl	Fe, Cu, Mn
Alkaloids	Berberine, Quinine	Nitrogen	Cu, Ag, Zn
Tannins	Hydrolysable tannins	Polyhydroxyl	Fe, Al, Cu
Coumarins	Umbelliferone	Carbonyl, Hydroxyl	Zn, Ni
Terpenoids	Ursolic acid	Hydroxyl, Carboxyl	Cu, Co

3. Synthesis of Plant-Derived Metal Coordination Complexes

The synthesis of plant-derived metal coordination complexes generally involves controlled reactions between purified phytochemicals or plant extracts and appropriate metal salts under optimized experimental conditions. The coordination process depends on several parameters including pH, solvent system, temperature, reaction time, ligand-to-metal ratio, oxidation state of the metal ion, and the chemical structure of the ligand [6]. Careful optimization of these factors is essential to obtain stable complexes with high purity, reproducibility, and desirable biological properties.

Conventional synthesis methods typically involve dissolving the plant-derived ligand and metal precursor separately in suitable solvents such as ethanol, methanol, water, dimethyl sulfoxide (DMSO), or mixed solvent systems. After controlled mixing under constant stirring, coordination occurs through ligand donor atoms interacting with vacant orbitals of the metal ion. The resulting complexes are subsequently purified by filtration, recrystallization, washing, and vacuum drying before structural characterization. Green synthesis has emerged as an environmentally sustainable alternative to traditional chemical methods. In this approach, crude plant extracts serve simultaneously as natural reducing agents, stabilizing agents, and complexing ligands, eliminating or substantially reducing the requirement for hazardous chemicals [7]. Polyphenols, flavonoids, sugars, proteins, amino acids, and organic acids present within plant extracts facilitate efficient coordination and stabilization of metal ions under mild reaction conditions.

Green synthesis not only reduces environmental impact but also often improves the biocompatibility and biological activity of the resulting complexes.

Microwave-assisted synthesis, ultrasound-assisted synthesis, mechanochemical synthesis, hydrothermal methods, and solvothermal techniques have further improved reaction efficiency by reducing reaction times, enhancing product yields, and improving crystal quality. These advanced synthetic approaches contribute to the development of coordination complexes with well-defined structural characteristics suitable for pharmaceutical applications. The choice of metal ion significantly influences coordination geometry, complex stability, electronic properties, redox behavior, and biological performance. Copper(II), zinc(II), iron(III), cobalt(II), nickel(II), manganese(II), ruthenium(III), silver(I), and vanadium(V) remain among the most extensively investigated metals because of their important biological roles and favorable coordination chemistry [8]. Optimization of synthesis conditions continues to be a major focus in medicinal inorganic chemistry to produce highly effective and pharmaceutically acceptable coordination compounds.

4. Structural Characterization of Plant-Derived Metal Coordination Complexes

Comprehensive structural characterization is essential for confirming the successful formation of plant-derived metal coordination complexes and understanding the relationship between their chemical structure and biological activity. Modern analytical techniques provide complementary information regarding molecular composition, coordination geometry, electronic structure, thermal stability, crystal morphology, particle size, and elemental composition [9]. The combination of spectroscopic, microscopic, thermal, and computational methods has greatly improved the reliability of structural investigations in coordination chemistry.

Ultraviolet-visible (UV–Vis) spectroscopy is commonly employed to investigate electronic transitions associated with ligand-to-metal charge transfer, d–d transitions, and complex formation. Coordination generally produces characteristic shifts in absorption maxima compared with free ligands, indicating successful metal binding.

Fourier-transform infrared (FTIR) spectroscopy provides valuable information regarding the participation of functional groups in metal coordination. Shifts in stretching frequencies corresponding to hydroxyl, carbonyl, carboxyl, amino, and methoxy groups indicate the donor atoms involved in complex formation.

Nuclear magnetic resonance (NMR) spectroscopy is widely used for diamagnetic coordination compounds to determine molecular structure and confirm ligand coordination. Changes in proton and carbon chemical shifts after complex formation provide evidence of metal–ligand interactions. Mass spectrometry further confirms molecular weight and composition while identifying fragmentation pathways that support structural elucidation [10]. Single-crystal X-ray diffraction remains the most definitive technique for determining the three-dimensional molecular structure of coordination complexes. It accurately reveals bond lengths, bond angles, coordination numbers, crystal packing, and molecular geometry. Powder X-ray diffraction (PXRD) is useful for evaluating crystallinity and phase purity when single crystals are unavailable.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide detailed information regarding particle morphology, size distribution, surface characteristics, and nanostructure. Energy-dispersive X-ray spectroscopy (EDX), coupled with SEM, confirms elemental composition and metal incorporation within the coordination complexes. Thermal characterization using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) evaluates thermal stability, decomposition behavior, coordinated water molecules, and phase transitions. Magnetic susceptibility measurements and electron paramagnetic resonance (EPR) spectroscopy provide additional information regarding oxidation states and electronic configurations of paramagnetic metal ions [11]. Density Functional Theory (DFT) calculations have become increasingly important for predicting molecular geometry, electronic structure, frontier molecular orbitals, molecular electrostatic potential, and reaction mechanisms. Computational chemistry complements experimental observations and facilitates rational design of coordination compounds with enhanced pharmaceutical properties.

Table 2: Characterization Techniques Used for Plant-Derived Metal Coordination Complexes

Technique	Information Obtained	Major Application
UV–Visible Spectroscopy	Electronic transitions	Confirmation of complex formation
FTIR Spectroscopy	Functional group coordination	Identification of donor atoms
NMR Spectroscopy	Molecular structure	Ligand characterization
Mass Spectrometry	Molecular weight	Molecular composition
X-ray Diffraction	Crystal structure	Coordination geometry
SEM and TEM	Morphology and particle size	Nanostructure analysis
EDX	Elemental composition	Metal confirmation
TGA and DSC	Thermal stability	Decomposition studies
DFT Calculations	Electronic structure	Computational modeling

5. Biological Activities of Plant-Derived Metal Coordination Complexes

The biological properties of plant-derived metal coordination complexes often exceed those of the corresponding free ligands due to synergistic interactions between metal ions and bioactive phytochemicals. Metal coordination modifies molecular geometry, electronic distribution, lipophilicity, redox potential, and membrane permeability, thereby enhancing pharmacological activity and improving therapeutic performance [12]. Antimicrobial activity represents one of the most extensively investigated properties of plant-derived metal complexes.

Copper, silver, zinc, cobalt, and nickel complexes synthesized from flavonoids, phenolic acids, alkaloids, and tannins exhibit broad-spectrum antibacterial and antifungal activities against both Gram-positive and Gram-negative microorganisms. Enhanced antimicrobial activity is generally attributed to increased membrane penetration, disruption of microbial enzymes, DNA interaction, oxidative stress induction, and inhibition of essential metabolic pathways.

Antioxidant activity is significantly influenced by the redox properties of coordinated metal ions. Complexation often enhances free radical scavenging capacity, inhibits lipid peroxidation, reduces oxidative stress, and protects cellular biomolecules from reactive oxygen species (ROS)-mediated damage. Flavonoid-metal complexes, particularly those containing copper and zinc, have demonstrated superior antioxidant activity compared with their parent phytochemicals [13]. Plant-derived metal complexes have also shown considerable promise as anticancer agents. Their mechanisms include DNA binding, inhibition of topoisomerases, induction of apoptosis, mitochondrial dysfunction, cell cycle arrest, angiogenesis inhibition, and modulation of intracellular signaling pathways. Copper, ruthenium, platinum, vanadium, and gallium complexes containing plant-derived ligands have demonstrated selective cytotoxicity against various human cancer cell lines while exhibiting lower toxicity toward normal cells. Anti-inflammatory activity is mediated through inhibition of cyclooxygenase (COX), lipoxygenase (LOX), nuclear factor kappa-B (NF-κB), pro-inflammatory cytokines, and oxidative stress pathways. Numerous flavonoid and polyphenol complexes reduce inflammation by regulating immune responses and suppressing inflammatory mediator production. Additional biological activities include antiviral, antidiabetic, antiparasitic, neuroprotective, hepatoprotective, cardioprotective, wound-healing, and immunomodulatory effects. These multifunctional biological properties make plant-derived metal coordination complexes promising candidates for the development of next-generation pharmaceuticals.

Table 3: Biological Activities of Plant-Derived Metal Coordination Complexes

Biological Activity	Common Metal Ions	Representative Plant Ligands	Major Mechanism
Antimicrobial	Cu, Ag, Zn	Quercetin, Berberine	Cell membrane disruption
Antioxidant	Cu, Zn, Mn	Catechin, Gallic acid	ROS scavenging
Anticancer	Cu, Ru, Pt	Curcumin, Quercetin	DNA interaction and apoptosis
Anti-inflammatory	Zn, Cu	Luteolin, Kaempferol	Cytokine inhibition
Antidiabetic	Vanadium, Zn	Caffeic acid	Enzyme regulation
Antiviral	Ag, Cu	Polyphenols	Viral enzyme inhibition
Neuroprotective	Zn, Mn	Flavonoids	Oxidative stress reduction

6. Pharmaceutical Applications

Plant-derived metal coordination complexes have emerged as promising therapeutic agents across multiple areas of pharmaceutical research owing to their enhanced stability, bioavailability, and pharmacological efficacy. In oncology, several coordination complexes are being investigated as alternatives to conventional chemotherapeutic agents because they exhibit improved selectivity toward cancer cells while reducing systemic toxicity. Metal–phytochemical complexes can target multiple cellular pathways simultaneously, decreasing the likelihood of drug resistance [14]. In antimicrobial therapy, these complexes provide an effective strategy for combating multidrug-resistant bacterial and fungal pathogens. Enhanced membrane permeability and multiple mechanisms of action make resistance development less likely compared with conventional antibiotics. This has generated considerable interest in developing metal-based phytopharmaceuticals for infectious disease management. Plant-derived coordination complexes also show promise in the treatment of inflammatory disorders, diabetes mellitus, neurodegenerative diseases, cardiovascular diseases, and oxidative stress-related conditions. Their ability to regulate oxidative balance, enzyme activity, and cellular signaling pathways contributes to broad therapeutic potential. Furthermore, controlled drug delivery systems incorporating metal coordination complexes are being developed to improve targeted drug release, enhance pharmacokinetics, and minimize adverse effects [15].

Nanotechnology has further expanded pharmaceutical applications by integrating plant-derived coordination complexes into nanoparticles, hydrogels, liposomes, and polymeric carriers. These advanced drug delivery platforms improve stability, tissue targeting, controlled release, and therapeutic efficacy while reducing toxicity. Such multifunctional systems represent an important direction in modern medicinal chemistry and pharmaceutical nanotechnology. The combination of green chemistry, medicinal inorganic chemistry, and nanomedicine continues to accelerate the translation of plant-derived metal coordination complexes into clinically relevant therapeutic agents.

7. Conclusion

Plant-derived metal coordination complexes represent a rapidly advancing area of medicinal inorganic chemistry, integrating the therapeutic potential of natural phytochemicals with the unique physicochemical and biological properties of metal ions. Complexation of bioactive plant compounds with essential and transition metals significantly enhances their chemical stability, solubility, bioavailability, membrane permeability, and pharmacological efficacy, thereby overcoming many limitations associated with free phytochemicals. The synergistic interactions between plant-derived ligands and metal centers have resulted in coordination compounds exhibiting broad-spectrum biological activities, including antimicrobial, antioxidant, anticancer, anti-inflammatory, antiviral, antidiabetic, neuroprotective, and immunomodulatory effects.

Advances in green chemistry have further promoted the sustainable synthesis of these complexes through environmentally friendly methodologies that minimize hazardous reagents and energy consumption while improving product safety and biocompatibility. At the same time, sophisticated analytical techniques such as UV–Visible spectroscopy, FTIR, NMR, mass spectrometry, X-ray diffraction, electron microscopy, thermal analysis, and computational modeling have greatly enhanced the structural characterization and mechanistic understanding of metal–ligand interactions. These developments have strengthened the rational design of coordination compounds with optimized biological performance and pharmaceutical potential, several challenges remain before widespread clinical application can be achieved. Issues related to large-scale synthesis, long-term chemical stability, pharmacokinetics, toxicity profiling, selective targeting, regulatory approval, and comprehensive clinical evaluation require further investigation. Standardized synthetic protocols, detailed mechanistic studies, and well-designed preclinical and clinical trials are essential to establish the safety, efficacy, and therapeutic value of these compounds. Moreover, greater emphasis should be placed on understanding structure–activity relationships and optimizing ligand design to improve selectivity and minimize adverse effects., plant-derived metal coordination complexes constitute a promising and sustainable platform for the development of innovative pharmaceutical agents. Their unique combination of natural product chemistry, coordination chemistry, and modern biomedical technologies positions them as valuable candidates for addressing current and emerging healthcare challenges, contributing significantly to future advances in drug discovery, medicinal chemistry, and personalized medicine.

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