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Medicinal Plant Phytochemicals as Natural Ligands for Metal Coordination Complexes: Advances in Bioinorganic Chemistry and Drug Discovery

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Abstract

Medicinal plants constitute one of the richest sources of structurally diverse phytochemicals that serve as promising natural ligands for the synthesis of metal coordination complexes with enhanced pharmacological activities. Bioactive compounds such as flavonoids, polyphenols, alkaloids, terpenoids, phenolic acids, tannins, coumarins, and glycosides possess functional groups capable of coordinating with biologically important metal ions, including copper, zinc, iron, cobalt, manganese, nickel, ruthenium, vanadium, and silver. Metal complexation often improves the physicochemical properties of phytochemicals by increasing their chemical stability, aqueous solubility, lipophilicity, bioavailability, and therapeutic efficacy while reducing toxicity. Recent advances in bioinorganic chemistry, medicinal chemistry, nanotechnology, and green synthesis have accelerated the development of plant-derived metal coordination complexes for applications in antimicrobial therapy, cancer treatment, antioxidant defense, anti-inflammatory therapy, antiviral research, and targeted drug delivery. Sophisticated analytical techniques including UV–Visible spectroscopy, Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), mass spectrometry (MS), X-ray diffraction (XRD), electron microscopy, thermogravimetric analysis (TGA), and computational modeling have substantially improved structural characterization and mechanistic understanding of these complexes. This review discusses the chemistry of medicinal plant phytochemicals as natural ligands, coordination mechanisms, synthesis strategies, structural characterization, biological activities, applications in drug discovery, current challenges, and future perspectives in medicinal bioinorganic chemistry.

Keywords: *Medicinal plants, Phytochemicals, Metal coordination complexes, Bioinorganic chemistry, Natural ligands, Drug discovery, Green synthesis.*

1. Introduction

Medicinal plants have been an indispensable source of therapeutic agents throughout the history of medicine, providing numerous bioactive compounds that continue to inspire the development of modern pharmaceuticals. More than 25% of currently available drugs are either directly derived from plants or developed from plant-derived lead molecules. Advances in phytochemistry have revealed an extraordinary diversity of secondary metabolites, including flavonoids, alkaloids, terpenoids, phenolic acids, tannins, coumarins, saponins, lignans, and glycosides, many of which exhibit potent biological activities. In recent years, these phytochemicals have attracted considerable attention in bioinorganic chemistry because of their ability to function as natural ligands capable of coordinating with biologically relevant metal ions [1].

Coordination chemistry involves the formation of stable complexes through coordinate covalent bonds between electron-donating ligands and metal ions. Medicinal plant phytochemicals possess multiple donor atoms such as oxygen, nitrogen, and sulfur present in hydroxyl, carbonyl, carboxyl, amino, methoxy, and thiol functional groups. These donor sites readily interact with transition metals, resulting in coordination complexes with modified electronic structures, enhanced redox properties, improved membrane permeability, and increased biological activity.

The combination of natural phytochemicals with metal ions has generated a rapidly expanding area of medicinal bioinorganic chemistry. Metal coordination frequently enhances the pharmacological properties of plant-derived compounds by improving chemical stability, protecting against metabolic degradation, increasing lipophilicity,

facilitating cellular uptake, and promoting controlled release of active species. Such complexes have demonstrated promising antimicrobial, anticancer, antioxidant, anti-inflammatory, antiviral, antidiabetic, neuroprotective, and antiparasitic activities [2]. The growing emphasis on sustainable chemistry has also stimulated interest in environmentally friendly synthesis methods. Green synthesis approaches utilize plant extracts as reducing agents, stabilizers, and ligand sources, thereby minimizing hazardous chemicals and reducing environmental impact. Simultaneously, developments in nanotechnology have enabled the incorporation of plant-derived coordination complexes into advanced drug delivery systems that improve therapeutic efficacy and target specificity. Recent advances in spectroscopic characterization, computational chemistry, molecular docking, and systems pharmacology have strengthened the understanding of metal–ligand interactions and facilitated rational drug design [3]. This review provides a comprehensive overview of medicinal plant phytochemicals as natural ligands for metal coordination complexes, emphasizing their chemistry, biological significance, pharmaceutical applications, and future prospects in drug discovery.

2. Medicinal Plant Phytochemicals as Natural Ligands

Medicinal plants produce a wide variety of secondary metabolites that function as highly effective natural ligands because of their structural diversity and abundance of electron-donating functional groups. These compounds have evolved as protective molecules against environmental stress, pathogens, herbivores, and oxidative damage, while simultaneously exhibiting important pharmacological activities in humans. Their ability to coordinate with metal ions has become a central focus in medicinal inorganic chemistry, where naturally occurring ligands are increasingly preferred over synthetic counterparts due to their biocompatibility, biodegradability, and lower toxicity. Flavonoids represent one of the largest and most extensively investigated classes of natural ligands. Compounds such as quercetin, kaempferol, luteolin, rutin, catechin, apigenin, and hesperidin contain multiple hydroxyl and carbonyl groups capable of chelating transition metal ions through stable five- or six-membered coordination rings. Metal complexation enhances their antioxidant activity by improving free radical scavenging capacity and stabilizing reactive intermediates. In addition, flavonoid-metal complexes have demonstrated superior antimicrobial, anticancer, and anti-inflammatory properties compared with the corresponding free flavonoids [4]. Phenolic acids, including gallic acid, caffeic acid, chlorogenic acid, ferulic acid, and ellagic acid, also function as excellent ligands because of their hydroxyl and carboxyl groups. These compounds readily coordinate with copper, iron, manganese, zinc, and other biologically important metals, producing complexes with improved redox behavior and enhanced pharmacological efficacy. Similarly, tannins possess numerous phenolic hydroxyl groups that provide exceptionally high metal-binding capacity, making them useful in antioxidant and antimicrobial applications.

Nitrogen-containing alkaloids represent another important class of medicinal plant ligands. Molecules such as berberine, quinine, morphine, colchicine, nicotine, and caffeine coordinate primarily through heterocyclic nitrogen atoms. Their metal complexes exhibit enhanced DNA-binding affinity, enzyme inhibition, antimicrobial activity, and cytotoxicity against cancer cells. Terpenoids, coumarins, lignans, xanthones, anthraquinones, and sulfur-containing phytochemicals further expand the diversity of naturally occurring ligands available for coordination chemistry [5]. The coordination behavior of phytochemicals depends upon the number and spatial arrangement of donor atoms, ligand flexibility, electronic effects, pH, solvent environment, oxidation state of the metal ion, and reaction conditions. Careful selection of both ligand and metal enables rational design of multifunctional coordination complexes with desirable physicochemical and biological properties.

Table 1: Major Classes of Medicinal Plant Phytochemicals Used as Natural Ligands

Phytochemical Class	Representative Compounds	Major Donor Atoms	Common Coordinating Metals	Major Biological Activities
Flavonoids	Quercetin, Kaempferol, Rutin	O	Cu, Zn, Fe, Co	Antioxidant, anticancer
Phenolic acids	Gallic acid, Caffeic acid	O	Fe, Cu, Mn	Antioxidant, antimicrobial
Alkaloids	Berberine, Quinine	N	Cu, Ag, Zn	Antimicrobial, anticancer
Tannins	Tannic acid	O	Fe, Al, Cu	Antioxidant
Coumarins	Umbelliferone	O	Zn, Ni	Anti-inflammatory
Terpenoids	Ursolic acid	O	Cu, Co	Anticancer
Glycosides	Digoxin derivatives	O	Zn, Fe	Cardioprotective

3. Coordination Chemistry of Plant-Derived Ligands

The coordination chemistry of medicinal plant phytochemicals is governed by the interaction between electron-rich donor atoms and vacant orbitals of metal ions. Most plant-derived ligands act as mono-, bi-, or polydentate ligands depending on the number and arrangement of donor atoms within their molecular structures. Oxygen atoms present in hydroxyl, carbonyl, carboxyl, and ether groups are the most common coordination sites, whereas nitrogen atoms in alkaloids and sulfur atoms in sulfur-containing phytochemicals also contribute significantly to metal binding. Transition metal ions including copper(II), zinc(II), iron(III), cobalt(II), nickel(II), manganese(II), ruthenium(III), vanadium(V), and silver(I) readily coordinate with medicinal plant ligands because of

their variable oxidation states and flexible coordination geometries [6]. These complexes commonly adopt octahedral, tetrahedral, square planar, or trigonal bipyramidal configurations depending on the electronic characteristics of the metal center and ligand architecture. Chelation generally increases the lipophilicity of the ligand by reducing the polarity of the metal ion through partial sharing of positive charge with donor atoms. Enhanced lipophilicity facilitates membrane permeability, improving intracellular uptake and increasing biological activity. Coordination also modifies redox potential, electronic distribution, and molecular geometry, enabling stronger interactions with enzymes, nucleic acids, membrane proteins, and cellular receptors.

The stability of coordination complexes depends on ligand denticity, chelate ring formation, steric effects, electronic factors, solution pH, temperature, solvent polarity, and competing biological ligands. Thermodynamic stability constants and kinetic stability determine the suitability of coordination complexes for pharmaceutical applications. Rational manipulation of these parameters allows the development of highly stable and biologically active metal–phytochemical complexes. Recent advances in computational chemistry, molecular docking, density functional theory (DFT), and molecular dynamics simulations have provided detailed insights into coordination mechanisms, electronic structures, binding energies, and biological interactions. These computational approaches complement experimental investigations and accelerate the discovery of novel plant-derived coordination compounds for therapeutic applications.

4. Structural Characterization of Plant-Derived Metal Coordination Complexes

Comprehensive structural characterization is essential for confirming successful coordination between medicinal plant phytochemicals and metal ions, determining coordination geometry, evaluating physicochemical properties, and establishing structure–activity relationships. Since the biological behavior of coordination complexes is strongly influenced by their molecular structure, modern analytical techniques provide indispensable information regarding bonding, crystallinity, thermal stability, particle morphology, oxidation state, and electronic configuration. The integration of spectroscopic, microscopic, thermal, and computational techniques enables accurate structural elucidation and supports the rational design of biologically active coordination compounds. Ultraviolet-visible (UV–Visible) spectroscopy is widely employed to monitor complex formation through characteristic changes in electronic absorption spectra. Coordination of phytochemical ligands with transition metal ions frequently produces bathochromic or hypsochromic shifts in absorption maxima due to ligand-to-metal charge transfer and d–d electronic transitions. Fourier-transform infrared (FTIR) spectroscopy is another indispensable technique that identifies functional groups involved in coordination [7]. Significant shifts in hydroxyl, carbonyl, carboxylate, amino, and methoxy stretching frequencies confirm the participation of donor atoms in metal binding and provide valuable information regarding coordination modes.

Nuclear magnetic resonance (NMR) spectroscopy is extensively applied to diamagnetic coordination complexes for determining molecular structure and ligand environment. Changes in proton (^1H) and carbon (^13C) chemical shifts after coordination indicate alterations in electron density around donor atoms. Mass spectrometry further confirms molecular composition, molecular weight, fragmentation patterns, and isotopic distribution, thereby supporting structural identification.

X-ray diffraction techniques remain the gold standard for determining the three-dimensional structure of coordination complexes. Single-crystal X-ray diffraction provides precise information regarding bond lengths, bond angles, coordination number, crystal packing, and molecular geometry. Powder X-ray diffraction (PXRD) is frequently employed when suitable single crystals are unavailable and assists in evaluating crystallinity, phase purity, and nanoparticle formation. Microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) provide detailed information regarding particle morphology, size distribution, surface characteristics, and nanostructure. Coupled with energy-dispersive X-ray spectroscopy (EDX), these methods also confirm elemental composition and successful incorporation of metal ions within the complexes [8]. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) evaluate thermal stability, coordinated water molecules, decomposition temperatures, and phase transitions. Electron paramagnetic resonance (EPR), magnetic susceptibility measurements, X-ray photoelectron spectroscopy (XPS), and density functional theory (DFT) calculations further contribute to understanding oxidation states, electronic structure, spin configuration, and metal–ligand interactions. Together, these complementary analytical techniques provide comprehensive characterization essential for pharmaceutical development.

Table 2: Analytical Techniques Used for Structural Characterization

Technique	Information Obtained	Application
UV–Visible Spectroscopy	Electronic transitions	Confirmation of complex formation
FTIR Spectroscopy	Functional group coordination	Identification of donor atoms
NMR Spectroscopy	Molecular structure	Ligand environment
Mass Spectrometry	Molecular weight	Molecular composition
Single-Crystal XRD	Crystal structure	Coordination geometry
Powder XRD	Crystallinity	Phase identification
SEM	Surface morphology	Particle characterization
TEM	Particle size	Nanostructure analysis
EDX	Elemental composition	Metal confirmation
TGA/DSC	Thermal stability	Decomposition studies
XPS	Oxidation state	Surface chemistry
DFT Calculations	Electronic structure	Computational modeling

5. Biological Activities of Metal–Phytochemical Coordination Complexes

Complexation of medicinal plant phytochemicals with transition metal ions frequently enhances their biological activities through synergistic interactions between the organic ligand and the coordinated metal center. Chelation modifies the physicochemical properties of phytochemicals by increasing lipophilicity, membrane permeability, redox activity, and metabolic stability, thereby improving pharmacological efficacy. Numerous studies have demonstrated that metal coordination complexes exhibit greater biological potency than their corresponding free ligands. Antimicrobial activity represents one of the most extensively investigated applications of plant-derived metal complexes. Copper, silver, zinc, cobalt, nickel, and manganese complexes synthesized from flavonoids, phenolic acids, alkaloids, and tannins exhibit broad-spectrum antibacterial and antifungal activity against both Gram-positive and Gram-negative microorganisms [9]. Their mechanisms involve disruption of microbial cell membranes, inhibition of essential enzymes, generation of reactive oxygen species, DNA damage, and interference with microbial protein synthesis. Because these complexes often target multiple cellular pathways simultaneously, they show promise for combating antimicrobial resistance.

Antioxidant activity is another important pharmacological property enhanced through metal coordination. Flavonoid-metal complexes exhibit superior free radical scavenging capacity by stabilizing reactive oxygen species, inhibiting lipid peroxidation, and protecting proteins, nucleic acids, and cellular membranes from oxidative damage. Zinc, copper, and manganese complexes have shown remarkable efficacy in reducing oxidative stress associated with aging, neurodegeneration, cardiovascular diseases, and inflammatory disorders. Plant-derived metal coordination complexes have also emerged as promising anticancer agents. Their mechanisms include DNA intercalation, inhibition of topoisomerases, induction of apoptosis, mitochondrial dysfunction, cell cycle arrest, angiogenesis inhibition, and modulation of intracellular signaling pathways. Copper, ruthenium, platinum, and vanadium complexes containing curcumin, quercetin, berberine, and other phytochemicals demonstrate selective cytotoxicity toward cancer cells while exhibiting relatively low toxicity toward normal tissues [10]. Additional biological activities include anti-inflammatory, antiviral, antidiabetic, antiparasitic, neuroprotective, hepatoprotective, cardioprotective, and immunomodulatory effects. These diverse pharmacological properties result from the ability of metal coordination complexes to regulate enzyme activity, inflammatory mediators, oxidative stress pathways, and gene expression. Consequently, plant-derived metal complexes represent attractive candidates for multifunctional therapeutic agents.

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

Biological Activity	Representative Metal Ions	Common Plant Ligands	Major Mechanism of Action
Antimicrobial	Cu, Ag, Zn	Quercetin, Berberine	Cell membrane disruption
Antioxidant	Cu, Zn, Mn	Catechin, Gallic acid	Free radical scavenging
Anticancer	Cu, Ru, Pt	Curcumin, Quercetin	DNA interaction and apoptosis
Anti-inflammatory	Zn, Cu	Kaempferol, Luteolin	Cytokine inhibition
Antidiabetic	V, Zn	Caffeic acid	Enzyme modulation
Antiviral	Ag, Cu	Polyphenols	Viral enzyme inhibition
Neuroprotective	Zn, Mn	Flavonoids	Reduction of oxidative stress
Hepatoprotective	Fe, Zn	Silymarin	Cellular protection

6. Applications in Drug Discovery and Pharmaceutical Development

Medicinal plant phytochemicals coordinated with metal ions have emerged as valuable lead compounds in modern drug discovery because they combine the pharmacological advantages of natural products with the unique chemical properties of transition metals. The resulting coordination complexes frequently display improved absorption, enhanced stability, prolonged circulation time, greater target selectivity, and superior therapeutic efficacy compared with free phytochemicals. In antimicrobial drug discovery, metal–phytochemical complexes are being investigated as next-generation agents capable of overcoming multidrug-resistant bacterial and fungal infections. Their multiple mechanisms of action reduce the likelihood of resistance development and provide broad-spectrum antimicrobial activity. Similarly, numerous plant-derived metal complexes have demonstrated promising anticancer activity by selectively targeting tumor cells while minimizing damage to healthy tissues [11]. The pharmaceutical industry is increasingly exploring these complexes for the treatment of chronic inflammatory diseases, diabetes mellitus, neurodegenerative disorders, cardiovascular diseases, and viral infections. Advances in medicinal chemistry have facilitated the optimization of ligand structure, coordination geometry, and metal selection to maximize biological activity while reducing toxicity. Nanotechnology has further expanded the pharmaceutical applications of plant-derived coordination complexes. Incorporation into nanoparticles, liposomes, polymeric nanocarriers, hydrogels, dendrimers, and biodegradable scaffolds improves targeted drug delivery, controlled release, pharmacokinetics, and tissue-specific accumulation. Such multifunctional delivery systems offer significant potential for precision medicine and personalized therapeutics. Recent integration of computational chemistry, molecular docking, artificial intelligence, and quantitative structure–activity relationship (QSAR) analysis has accelerated the identification and optimization of novel coordination compounds. These computational approaches reduce experimental costs and facilitate rational design of highly effective plant-derived metal-based pharmaceuticals.

7. Green Synthesis of Plant-Derived Metal Coordination Complexes

Green synthesis has emerged as an environmentally sustainable and economically attractive approach for preparing metal coordination complexes using medicinal plant phytochemicals.

Unlike conventional synthetic methods that often require hazardous organic solvents, toxic reducing agents, and energy-intensive reaction conditions, green synthesis utilizes naturally occurring phytochemicals as reducing agents, stabilizing agents, chelating ligands, and capping molecules. This approach aligns with the principles of green chemistry by minimizing environmental pollution, reducing chemical waste, improving energy efficiency, and promoting the use of renewable biological resources [12]. Medicinal plant extracts contain a diverse mixture of bioactive constituents, including flavonoids, polyphenols, tannins, alkaloids, terpenoids, sugars, amino acids, proteins, and organic acids, which collectively facilitate the reduction and coordination of metal ions under mild reaction conditions. During synthesis, these phytochemicals donate electron pairs through oxygen, nitrogen, or sulfur atoms, forming stable coordination complexes while simultaneously preventing aggregation and enhancing long-term stability. The resulting complexes often exhibit improved biocompatibility, reduced toxicity, and enhanced biological activity compared with complexes synthesized using conventional chemical methods. Several medicinal plants, including *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Azadirachta indica* (neem), *Moringa oleifera*, *Ocimum sanctum* (holy basil), *Terminalia chebula*, *Punica granatum* (pomegranate), and *Aloe vera*, have been successfully employed for the green synthesis of metal coordination complexes. Copper, zinc, silver, iron, cobalt, manganese, nickel, and gold complexes prepared using these plant extracts have demonstrated significant antimicrobial, antioxidant, anticancer, anti-inflammatory, and wound-healing properties.

The green synthesis process is influenced by several reaction parameters, including plant species, phytochemical composition, extraction solvent, pH, temperature, reaction time, metal ion concentration, and ligand-to-metal ratio. Optimization of these factors is essential to produce coordination complexes with desirable physicochemical characteristics, reproducibility, and biological performance. Green synthesis has also facilitated the integration of medicinal plant coordination complexes with nanotechnology. Plant-mediated metal complexes incorporated into nanoparticles, nanocomposites, hydrogels, and biodegradable polymers have demonstrated improved targeted drug delivery, controlled release, enhanced pharmacokinetics, and reduced systemic toxicity. Consequently, green synthesis has become an important strategy for sustainable pharmaceutical development and environmentally responsible medicinal chemistry.

Table 4: Green Synthesis of Plant-Derived Metal Coordination Complexes

Medicinal Plant	Major Phytochemicals	Metal Ions	Potential Biomedical Applications
Curcuma longa	Curcumin	Cu, Zn, Fe	Anticancer, antioxidant
Camellia sinensis	Catechins	Ag, Cu	Antimicrobial
Azadirachta indica	Flavonoids, Limonoids	Ag, Zn	Antibacterial, wound healing
Moringa oleifera	Polyphenols	Fe, Cu	Antioxidant
Ocimum sanctum	Eugenol, Flavonoids	Zn, Cu	Anti-inflammatory
Punica granatum	Ellagic acid	Ag, Fe	Antioxidant, antimicrobial
Aloe vera	Anthraquinones	Cu, Zn	Tissue regeneration

9. Conclusion

Medicinal plant phytochemicals represent an exceptionally valuable source of natural ligands for the synthesis of biologically active metal coordination complexes. Their structural diversity, abundance of oxygen-, nitrogen-, and sulfur-containing donor groups, and intrinsic pharmacological properties make them highly suitable for coordination with biologically important metal ions. Complexation significantly improves the physicochemical characteristics of phytochemicals, including chemical stability, aqueous solubility, lipophilicity, membrane permeability, bioavailability, and metabolic resistance, ultimately enhancing their therapeutic potential.

Recent advances in bioinorganic chemistry, medicinal chemistry, and green synthesis have substantially expanded the scope of plant-derived metal coordination complexes in drug discovery. Numerous complexes synthesized from flavonoids, phenolic acids, alkaloids, tannins, coumarins, terpenoids, and other phytochemicals have demonstrated remarkable antimicrobial, antioxidant, anticancer, anti-inflammatory, antiviral, antidiabetic, neuroprotective, and immunomodulatory activities. Their multifunctional mechanisms of action, combined with relatively low toxicity and improved pharmacokinetic properties, position these compounds as promising candidates for next-generation therapeutics. Modern analytical techniques, including UV–Visible spectroscopy, FTIR, NMR, mass spectrometry, X-ray diffraction, electron microscopy, thermal analysis, and computational modeling, have greatly enhanced structural characterization and understanding of metal–ligand interactions. Simultaneously, green chemistry approaches have provided environmentally sustainable methods for synthesizing coordination complexes while minimizing hazardous reagents and promoting renewable biological resources.

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