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The Role of Copper Complexes in Drug Development: From Synthesis to Clinical Prospects

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Abstract

Copper complexes are gaining attention in drug development due to their unique properties and potential applications in various therapeutic areas, particularly in cancer treatment and neurodegenerative diseases. Unlike traditional platinum-based drugs like cisplatin, which bind to DNA and often lead to severe side effects and drug resistance, copper complexes offer alternative mechanisms of action. They can enhance cellular uptake and induce apoptosis through diverse pathways, potentially resensitizing resistant cancer cells to platinum therapies. Additionally, copper's role in promoting tumor growth and angiogenesis highlights its therapeutic potential, as specific chelators and ionophores can selectively target cancer cells, providing a more favorable therapeutic window with reduced toxicity. In the realm of neurodegenerative diseases, copper complexes are being explored for their ability to modulate copper homeostasis, which is crucial for preventing neurodegenerative processes associated with conditions like Alzheimer's disease. They can disrupt metal-Aβ interactions and regulate redox homeostasis, thereby reducing neurotoxicity. Furthermore, novel approaches, such as the use of peptoid-based chelators, aim to enhance selectivity in targeting copper over other metals like zinc, which is also present in the synaptic cleft. The versatility of copper complexes extends to their antimicrobial properties, where they can disrupt bacterial membranes and inhibit protein synthesis, making them effective against various pathogens. Overall, the ongoing research into copper complexes underscores their potential as effective agents in addressing significant health challenges, including cancer, neurodegenerative diseases, and multidrug-resistant infections, paving the way for innovative therapeutic strategies in drug development.

Keywords: Copper Complexes, Drug Development, Neurodegenerative Diseases, Chelation Therapy, Antimicrobial Properties, Bioavailability.

Introduction

Copper is an essential trace element in human physiology, serving as a cofactor for numerous enzymes critical to various biological processes. Key enzymes that require copper include cytochrome c oxidase, superoxide dismutase (SOD), dopamine-β-hydroxylase, lysyl oxidase, and ceruloplasmin, among others. Cytochrome c oxidase is vital for cellular respiration, facilitating the electron transport chain in mitochondria, which is crucial for ATP production (1)(2). Superoxide dismutase plays a significant role in antioxidant defense by catalyzing the dismutation of superoxide radicals into oxygen and hydrogen peroxide, thus protecting cells from oxidative damage (3)(2). Dopamine-β-hydroxylase is involved in neurotransmitter biosynthesis, converting dopamine to norepinephrine, which is essential for proper neuronal function and development (1)(4). Lysyl oxidase contributes to connective tissue formation by catalyzing the cross-linking of collagen and elastin, which is crucial for maintaining the structural integrity of tissues (2)(5). Ceruloplasmin, a copper-carrying protein, is involved in iron homeostasis, facilitating iron transport and preventing iron-induced oxidative stress (2)(6). The regulation of copper levels is

critical, as both deficiency and excess can lead to severe health issues. Disorders such as Menkes disease and Wilson disease illustrate the consequences of disrupted copper homeostasis, leading to neurological and systemic pathologies due to the malfunction of copper-dependent enzymes (1)(5)(6). Copper transporters like ATP7A and ATP7B are essential for maintaining copper balance, ensuring its proper distribution and preventing toxicity (7)(8).

Copper plays a crucial role in biological systems, but its redox properties can lead to oxidative stress, contributing to various disease pathways, including cancer, neurodegeneration, and infections. Copper homeostasis is tightly regulated through a network of transporters and chaperones to prevent its accumulation and the resultant oxidative damage (9)(10). In neurodegenerative diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, copper's ability to generate reactive oxygen species (ROS) exacerbates oxidative stress, leading to mitochondrial dysfunction and neuroinflammation (9)(11). Copper can aberrantly bind to proteins like alpha-synuclein and tau, promoting protein misfolding and neurotoxicity (9). Additionally, copper's involvement in apoptotic pathways further contributes to neurodegeneration (11)(12). In cancer, copper's role in cell signaling pathways is significant, as it modulates key enzymes and influences cellular mechanisms, potentially driving tumorigenesis (13). The novel concept of cuproptosis, a copper-dependent form of cell death, highlights copper's dual role in both promoting and potentially treating cancer by targeting copper-protein interactions (14). Furthermore, copper's interaction with peptides can lead to both pathogenic and therapeutic outcomes, as these complexes can damage biological macromolecules or exhibit antibacterial and anticancer properties (15). In infections, copper's antimicrobial properties are harnessed, but its dysregulation can also facilitate disease progression (15).

Copper complexes offer several advantages over traditional organic drugs in pharmaceuticals, particularly due to their redox activity, multiple coordination modes, and ability to bind with DNA and proteins. The redox properties of copper allow it to cycle between +1 and +2 oxidation states, facilitating the generation of reactive oxygen species (ROS) that induce oxidative stress selectively in cancer cells, which are more vulnerable to such stress than normal cells (16)(17). This redox activity is a key mechanism in the cytotoxic action of copper complexes, making them effective anticancer agents (18)(19). Furthermore, the coordination versatility of copper enables the formation of diverse complexes with tailored functionalities, enhancing their biological activity and allowing for fine-tuning of pharmacological properties by varying ligands and donor atoms (20)(21). Copper complexes can interact with nucleic acids, particularly DNA, through mechanisms similar to those of cisplatin, but with potentially fewer side effects and reduced resistance issues (22)(17). This interaction often involves binding to DNA bases, leading to DNA damage and apoptosis in cancer cells (22). Additionally, copper complexes have shown broad-spectrum pharmacological activities, including antimicrobial, antituberculosis, antimalarial, antifungal, and anti-inflammatory effects, making them versatile therapeutic agents (21)(23). Their ability to modulate copper homeostasis also provides protective effects in neurodegenerative diseases and other conditions, further highlighting their therapeutic potential (18).

Copper complexes are emerging as promising alternatives to platinum-based drugs like cisplatin in cancer therapy, primarily due to their distinct mechanisms of action and ability to address limitations

associated with platinum drugs, such as toxicity and drug resistance. While cisplatin operates by binding to nuclear DNA, leading to cell death, it suffers from severe side effects and the development of resistance through altered copper homeostasis in cancer cells (24)(25). In contrast, copper complexes, particularly those with dithiocarbamate ligands, can enhance cellular uptake and induce apoptosis through diverse pathways, potentially re-sensitizing resistant cancer cells to platinum treatments (24)(26). Furthermore, copper's role in promoting tumor growth and angiogenesis highlights its therapeutic potential, as copper-specific chelators and ionophores can selectively target cancer cells, offering a more favorable therapeutic window and reduced toxicity compared to traditional platinum therapies (27)(26).

Copper complexes have emerged as promising agents in drug development, particularly in cancer therapy, due to their unique properties and mechanisms of action. They can effectively overcome multidrug resistance (MDR) in cancer cells by inducing various forms of cell death, such as apoptosis and oncosis, through mechanisms like disrupting copper homeostasis and generating reactive oxygen species (ROS). Notably, di-2-pyridylketone thiosemicarbazones and apoferritin-encapsulated copper complexes have shown efficacy in targeting cancer cells, including those resistant to conventional therapies. Additionally, copper-NSAID complexes have been designed to specifically target cancer stem cells, enhancing their therapeutic potential. Beyond oncology, copper chelation therapies are being explored for neurodegenerative diseases like Alzheimer's and Parkinson's, where they aim to restore metal homeostasis and reduce neurotoxicity. Despite the promising preclinical results, challenges remain in translating these copper complexes into clinical settings, primarily due to issues like copper leaching and biological speciation. Overall, the versatility and unique mechanisms of copper complexes position them as compelling alternatives to traditional chemotherapeutics, warranting further research and development.

Synthesis and Design Strategies for Copper Complexes

The synthesis and design of copper complexes involve strategic ligand selection and coordination chemistry, with common ligands including Schiff bases, thiosemicarbazones, polypyridyls, and peptides. Schiff bases, formed from the condensation of amino and carbonyl compounds, are versatile ligands that coordinate to copper ions via azomethine nitrogen, offering diverse applications in catalysis, biological systems, and pharmaceuticals (28)(29). These ligands can form various coordination geometries, such as square planar and octahedral, depending on the ligand's denticity and the presence of additional coordinating groups (30)(31). Thiosemicarbazones, another important class, exhibit polydentate coordination through S-N-O sites, forming stable complexes with copper that are often square planar and have significant biological activities, including antibacterial and anticancer properties (32)(33). Polypyridyl ligands, such as 2,2′-dipyridyldisulfide, facilitate the formation of copper complexes with diverse structural motifs, including helical and sheet structures, due to their flexible coordination modes (34). These ligands are crucial in designing copper complexes with specific properties and functions, as they influence the geometry, stability, and reactivity of the complexes. The coordination chemistry of these ligands with copper is extensively studied for its potential in developing new materials and therapeutic agents, highlighting the importance of ligand selection in the synthesis of copper complexes (35)(36)(37).

The selection of ligands in the synthesis of copper complexes significantly influences their stability, solubility, and bioavailability, which are crucial for their potential applications in medicine and biology. Ligands such as phenanthroline and histidine derivatives have been shown to form stable copper(II) complexes with high stability across a wide pH range, which is essential for maintaining their structure and function in biological environments (38). Bis(thiosemicarbazones) are another class of ligands that form stable, neutral copper complexes, which are particularly useful in radiopharmaceutical applications due to their ability to coordinate copper radioisotopes (39). Schiff bases, derived from aromatic carbonyl compounds and hydrazides, also form stable copper complexes, with their coordination geometry affecting their magnetic properties and potential biological activities (29)(35). The introduction of heterocyclic structures, such as flavone derivatives, enhances the solubility and lipophilicity of copper complexes, thereby improving their bioavailability and therapeutic potential (40). Additionally, the coordination geometry, such as the five-coordinate, distorted trigonal-bipyramidal structure, can enhance the metabolic stability of copper complexes, making them more resistant to redox-mediated structural changes (41). The choice of ligand and its structural modifications, such as the incorporation of electron-withdrawing groups, can further enhance the biological activity of copper complexes, making them promising candidates for combating multidrug-resistant organisms (40). the strategic selection and design of ligands are pivotal in tailoring the properties of copper complexes for specific biomedical applications, ensuring their stability, solubility, and bioavailability in physiological conditions (38)(39)(40)(41).

The synthesis and design strategies for copper complexes have been explored through various conventional routes, including solution chemistry and solvothermal synthesis, each offering unique advantages and challenges. Solution chemistry allows for the straightforward synthesis of copper complexes, as demonstrated by the use of 2,2′-dipyridyldisulfide (dpds) ligands to form diverse copper structures with different dimensionalities and coordination modes (34). This method is advantageous for its simplicity and the ability to yield complexes with specific structural features, such as helical chains and sheet structures (34). On the other hand, solvothermal synthesis provides a versatile approach to creating copper complexes with intricate architectures, such as the 18-membered macrocycle Schiff base dinuclear copper(II) complex, which exhibits a distorted octahedral geometry and is stabilized by hydrogen-bonding interactions (42). This method is particularly useful for synthesizing coordination polymers and frameworks, as seen in the formation of luminescent copper(I) thiocyanate coordination polymers with diverse structures ranging from one-dimensional chains to three-dimensional frameworks (43). Solvothermal synthesis also facilitates the creation of copper complexes with unique properties, such as antiferromagnetic interactions and luminescence, which are valuable for various applications (44)(45). Additionally, the use of N,N-heterocyclic derivatives and dipyridylamine ligands in copper complexes has been explored for their potential as photoredox catalysts, highlighting the importance of ligand design in enhancing the functional properties of copper complexes (46)(47).

The synthesis and design strategies for copper complexes have increasingly embraced green chemistry approaches, notably microwave-assisted and mechanochemical synthesis, due to their efficiency and environmental benefits.

Microwave-assisted synthesis is recognized for its rapid and energy-efficient process, significantly reducing reaction times and enhancing yields and purity of copper complexes. This method has been successfully applied in synthesizing copper(II) complexes with sulfonamides and bis-phosphonamides, demonstrating notable biological activities and structural insights through spectroscopic and computational analyses (48)(49). The versatility of microwave irradiation in synthesizing transition metal complexes, including copper, is highlighted by its ability to facilitate complex transformations with reduced decomposition risks (50). On the other hand, mechanochemical synthesis, particularly through ball milling, offers a solvent-free, scalable, and cost-effective route for producing copper complexes. This approach has been effectively utilized to synthesize N-heterocyclic carbene copper complexes and copper iodide-based hybrid phosphors, which exhibit high luminescence and potential for commercialization (51)(52). Mechanochemical methods also align with green chemistry principles by minimizing waste and energy consumption, as demonstrated in the synthesis of copper hydroxyphosphate (53). Both methods underscore the potential of copper complexes in various applications, from photopolymerization to nanotechnology, due to their favorable properties and the sustainable nature of their synthesis (54)(55).

Copper complexes exhibit significant structural diversity and can be classified into mononuclear and polynuclear forms, with varying oxidation states such as Cu(I), Cu(II), and mixed-valent systems. Mononuclear copper complexes often feature a square pyramidal geometry, as seen in complexes with Schiff-base ligands and pyridylalkylaminomethylphenol polypodal ligands, where the copper center is coordinated by phenolic oxygen in the axial position (56)(57). Polynuclear complexes, on the other hand, can range from dinuclear to polymeric forms, with structures such as trinuclear and tetranuclear arrangements, often bridged by ligands like phenoxo oxygens or thiocyanate, which contribute to their diverse geometries and functionalities (56)(58)(59). The oxidation states of copper in these complexes are crucial for their properties and reactivities. Cu(I) complexes, for instance, are known for their structural diversity, often forming discrete dimeric or polymeric structures with ligands like piperidine-2,6-dithione (60). Mixed-valent systems, such as those containing both Cu(I) and Cu(II), exhibit unique electronic properties, as demonstrated by the EPR spectra of certain trinuclear complexes (58). Cu(II) complexes are prevalent and can be stabilized in various geometries, including square planar and distorted octahedral, often exhibiting catalytic and antioxidant activities (61)(62). The design and synthesis of these complexes are influenced by ligand selection and reaction conditions, which can direct the formation of specific nuclearities and oxidation states, thereby tailoring the complexes for desired applications (63). the structural diversity and classification of copper complexes are deeply intertwined with their oxidation states, which dictate their chemical behavior and potential applications in catalysis and materials science.

Analytical Characterization Techniques

Copper complexes can be effectively characterized using various spectroscopic methods, including UV-Vis, IR, and EPR spectroscopy, which provide insights into their electronic and geometric structures. UV-Vis spectroscopy reveals electronic transitions and oxidation states, as seen in studies of copper(II) complexes with Schiff bases, where redox potentials indicate significant geometric changes during oxidation and reduction processes (64). IR

spectroscopy elucidates ligand coordination modes, demonstrating how amino acids act as bidentate ligands through carbonyl and amino group interactions (65). EPR spectroscopy is particularly valuable for understanding the local symmetry and electronic environment of copper ions, showing distinct patterns that reflect the geometry of the complexes, such as square planar or distorted tetrahedral arrangements (66) (67).

X-ray diffraction (XRD) and single-crystal X-ray diffraction (SC-XRD) are pivotal techniques for determining the molecular geometry and supramolecular interactions in copper complexes. These methods provide detailed insights into the structural arrangement and coordination environment of copper ions within complexes. For instance, the copper complex [Cu(DHBEE)2] was found to adopt a square planar geometry, with the Cu2+ ion occupying a center of inversion symmetry, as revealed by XRD analysis (68). Similarly, the bis[1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-ium-4-yl)-1,4-dihydroquinoline-3-carboxylato]copper(II) sulfate heptahydrate complex also exhibits a square-planar environment, with extensive hydrogen bonding networks stabilizing the structure (69). SC-XRD studies further elucidate the coordination geometry, as seen in the pentacoordinate polymeric copper(II) complex with 2-amino-2-methyl-1,3-propandiol, which displays a distorted square pyramidal geometry (70). These techniques also allow for the exploration of supramolecular interactions, such as hydrogen bonding and π–π stacking, which are crucial for the stability and assembly of the complexes (71). Additionally, XRD and SC-XRD can be complemented by other spectroscopic methods, such as FT-IR and EXAFS, to provide a comprehensive understanding of the electronic environment and bond lengths within the complexes (72)(73). these diffraction techniques are indispensable for characterizing the intricate details of copper complexes, offering insights into their potential applications in various fields.

Cyclic voltammetry is a powerful technique for studying the redox behavior of copper complexes, providing insights into their mechanisms of action. The electrochemical analysis of copper complexes with various ligands reveals diverse redox behaviors influenced by ligand type and coordination environment. For instance, copper complexes with 8-hydroxyquinoline exhibit two oxidation peaks at 0.154V and 0.60V, indicating a surface-controlled process with significant electrochemical activity, particularly in a 1:1 coordination state (74). Similarly, copper complexes with benzimidazole and thioether ligands show that sulfur-rich environments have higher Cu(2+)/Cu(+) redox potentials, with initial oxidation occurring at the sulfur atom, suggesting ligand-based redox processes (75). In organic solvents, copper(II) benzimidazole complexes undergo a quasi-reversible Cu(2+)/Cu(+) redox step followed by an irreversible reduction to metallic copper (76). Copper(II) complexes with chloro and bromo ligands also display two-step redox processes, with the first step being quasi-reversible and diffusion-controlled (77). The influence of ligands is further highlighted in copper(II)-carboxylate complexes, where the redox processes are similarly two-stepped, involving a quasi-reversible and an irreversible step (78). In dimethylsulfoxide, copper complexes with tetramethylethylenediamine exhibit two-stage diffusion-controlled reductions, with the first redox couple showing weak adsorption of the electrogenerated species (79). Additionally, copper complexes with Schiff base ligands demonstrate excellent electrocatalytic behavior for CO2 activation, with ligand-based redox processes (80). Mixed-ligand copper complexes involving 2,2'-bipyridine and amino acids also show quasi-reversible Cu(2+)/Cu(+) redox changes, with EPR

spectra supporting these findings (81). The redox potential of copper complexes used in atom transfer radical polymerization is influenced by the ligand and halogen, correlating with their catalytic efficiency (82). Finally, thiosemicarbazone complexes exhibit redox properties affected by substituents, with electron-withdrawing groups stabilizing the Cu(II) state and electron-donating groups favoring oxidation to Cu(III) (83).

Copper complexes have been extensively studied using computational modeling techniques such as Density Functional Theory (DFT) and molecular docking to predict their reactivity, stability, and interactions with biomolecules. DFT calculations provide insights into the electronic structure and stability of copper complexes, as seen in the study of trans-[Cu(quin)2(EtOH)2], which revealed a stable structure with a moderate band gap and potential sites for protein interactions through molecular electrostatic potential mapping (84). Similarly, DFT was used to optimize the geometry and analyze the frontier molecular orbitals of copper complexes, aiding in understanding their reactivity and interaction sites (85). Molecular docking studies complement these findings by simulating the binding of copper complexes to biological targets. For instance, copper complexes have shown strong binding affinities to DNA and proteins, indicating potential therapeutic applications. The binding modes often involve groove binding or intercalation, as demonstrated in studies involving copper complexes with DNA and bovine serum albumin (BSA) (86)(87). Additionally, copper complexes have been evaluated for their biological activities, including antimicrobial and anticancer properties. For example, certain copper complexes exhibited significant antibacterial activity against pathogens like Bacillus cereus and Staphylococcus aureus, and anticancer activity against breast adenocarcinoma cells (84)(88). The integration of DFT and molecular docking provides a comprehensive approach to understanding the multifaceted roles of copper complexes in biological systems, highlighting their potential as therapeutic agents with enzyme-like activities and biomolecular interactions (89)(87).

Mechanisms of Action and Biological Targets

Copper complexes have emerged as promising candidates in anticancer therapy due to their ability to interact with DNA through various mechanisms, including intercalation, groove binding, and oxidative DNA cleavage. These interactions are crucial for their anticancer activity. Intercalation involves the insertion of planar aromatic ligands between DNA base pairs, which is a common mode of action for many copper complexes. For instance, complexes such as [Cu(Thr)(Phen)H2O]Cl·2H2O and [Cu(bpbb)0.5·Cl·SCN]·(CH3OH) have demonstrated strong intercalative binding to DNA, which is supported by absorption spectral titration and ethidium bromide displacement assays (90)(91). Groove binding, on the other hand, involves the binding of copper complexes to the minor or major grooves of the DNA helix, as seen in the interaction of [Cu(Thr)(Byp)Cl]·H2O with calf-thymus DNA (90). Oxidative DNA cleavage is another significant mechanism, where copper complexes generate reactive oxygen species (ROS) that induce DNA strand breaks. This activity is enhanced in the presence of activators like ascorbic acid or hydrogen peroxide, as observed in complexes such as Cu(L2)2·2DMF and Cu(L3)2·2DMF, which exhibit oxidative cleavage of supercoiled plasmid DNA (92)(93). The generation of ROS not only causes DNA damage but also leads to cell cycle arrest and apoptosis, contributing to the cytotoxic effects against cancer cells (91)(94). Furthermore, the structural features of these complexes, such as the

presence of planar ligands and the geometry of the copper center, play a crucial role in determining their DNA binding affinity and cleavage efficiency (95). The anticancer potential of these complexes is further supported by their selective cytotoxicity towards cancer cells over normal cells, as demonstrated in various in vitro studies (92)(96).

Copper complexes have emerged as promising alternatives to cisplatin in anticancer therapy due to their diverse mechanisms of interaction with DNA and their potential to overcome the limitations associated with platinum-based drugs, such as severe side effects and drug resistance. Various studies have demonstrated that copper complexes can exhibit superior cytotoxicity compared to cisplatin, often through different modes of DNA interaction and cellular mechanisms. For instance, a copper complex coordinated with dipicolinic acid showed promising cytotoxic activity against HCT116 colon cell lines, with a non-intercalative binding mode to DNA, primarily involving hydrogen bonding and van der Waals forces, and demonstrated nuclease activity in the presence of H_2O_2 (97). Similarly, copper complexes with 4-chloro-3-nitrobenzoic acid ligands exhibited intercalative binding to DNA and induced apoptosis by regulating the Bcl-2 protein family, showing greater antitumor efficacy than cisplatin (98). Another study highlighted copper complexes with substituted terpyridine ligands that displayed significant intercalative binding with DNA and superior anticancer activity, with IC50 values lower than 2.5 μM across various cancer cell lines (99). Furthermore, adenine-based copper complexes demonstrated potent cytotoxic effects by inducing DNA damage, cell cycle arrest, and apoptosis through ROS production, surpassing cisplatin in efficacy (100). Copper complexes with quinoline-derived Schiff-base ligands also showed enhanced cytotoxicity, particularly against HeLa cells, by promoting apoptosis via a ROS-mediated mitochondrial pathway (101). Additionally, a cis-dichloridobis(diimine)copper(II) complex exhibited higher toxicity than cisplatin, inducing apoptosis in A549 cells (102). The dinuclear copper complex with phosphate ligands demonstrated strong cytotoxic effects and DNA synthesis inhibition, primarily interacting with phosphate diesters in the DNA backbone (103).

Copper complexes have emerged as promising agents in cancer therapy due to their ability to generate reactive oxygen species (ROS) through Fenton-like reactions, which can induce oxidative stress and apoptosis in cancer cells. These complexes, such as those containing 2-(1H-imidazol-2-yl)pyridine and amino acids, have shown the ability to interact with DNA and human serum albumin, leading to oxidative DNA cleavage and mitochondrial dysfunction, ultimately resulting in cancer cell apoptosis (104). The generation of ROS, including singlet oxygen, hydrogen peroxide, and superoxide anion radicals, is a key mechanism by which these copper complexes exert their anticancer effects (104). Additionally, copper-containing nanoparticles and organic complexes can trigger rapid cell death via oxidative bursts when combined with reducing agents like N-acetylcysteine, which facilitate the reduction of copper ions and subsequent ROS production (105). Innovative materials like copper nitroprusside have been developed to self-induce hydrogen peroxide and produce peroxynitrite, enhancing ROS generation at tumor sites and demonstrating potent antitumoral effects (106). The versatility of copper complexes is further highlighted by their ability to modulate glutathione levels, thereby amplifying ROS-mediated cancer therapies such as chemodynamic and photodynamic therapy (107). Moreover, copper complexes can target mitochondria, as seen with Cu(I)-based agents that

generate hydroxyl radicals through Fenton-like reactions, causing mitochondrial damage and enhancing therapeutic efficacy (108). The development of copper-diimine coordination compounds and their ability to bind DNA and generate ROS and reactive nitrogen species further underscores their potential as anticancer agents (17).

Copper complexes have emerged as promising agents for enzyme inhibition, particularly targeting proteases, kinases, and metalloenzymes such as superoxide dismutase (SOD) and cytochrome C oxidase. These complexes leverage the unique properties of copper, including its ability to exist in multiple oxidation states, which facilitates redox and catalytic activities essential for enzyme modulation (18). In cancer treatment, copper complexes have shown potential as proteasome inhibitors, specifically targeting the ubiquitin-proteasome pathway (UPP) to induce apoptosis in tumor cells. This is achieved through the selective inhibition of proteasome activity, which is crucial for protein regulation within cells (109)(110). Schiff base copper(II) complexes, for instance, have demonstrated cytotoxic effects against various cancer cell lines, including lung carcinoma and glioblastoma, by inhibiting proteasome activity and inducing cell death (110). Additionally, copper complexes have been developed to mimic the activity of SOD, a metalloenzyme that protects against oxidative stress by scavenging reactive oxygen species (ROS). These complexes offer a therapeutic advantage by overcoming the limitations of natural SOD, such as its short in vivo lifespan and poor cellular uptake (111). The structural diversity and adjustable ligand exchange kinetics of copper complexes allow for precise targeting and inhibition of enzyme active sites, enhancing their selectivity and efficacy as therapeutic agents (112)(113). Furthermore, copper complexes have been explored for their ability to modulate copper homeostasis in the brain, providing neuroprotective effects in models of neurodegeneration (18). the versatility and biological activity of copper complexes make them valuable candidates for developing novel enzyme inhibitors with applications in cancer therapy and beyond (23)(114).

Copper complexes exhibit significant antimicrobial and anti-inflammatory activities through various mechanisms, including membrane disruption, protein denaturation, and immune modulation. The antimicrobial action of copper complexes is primarily attributed to their ability to disrupt bacterial cell membranes, leading to increased permeability and eventual cell death. This is achieved through the generation of reactive oxygen species (ROS) that damage cellular components, including membranes and genetic material, thereby inhibiting bacterial growth and survival (115)(116)(117). Additionally, copper complexes can interfere with protein synthesis and enzymatic functions within bacterial cells, further enhancing their antimicrobial efficacy (115)(118). In terms of anti-inflammatory pathways, copper complexes have been shown to inhibit the production of superoxide anions, which are involved in inflammatory processes, thereby reducing inflammation (119). These complexes also stabilize cell membranes, preventing the release of inflammatory mediators (120). Moreover, copper plays a role in modulating immune responses, particularly through its involvement in macrophage antimicrobial pathways, where it can either enhance antimicrobial activity or limit metal availability to pathogens, thus contributing to host defense mechanisms (121). The therapeutic potential of copper complexes is further underscored by their ability to act as enzyme inhibitors and their cytotoxic effects on cancer cells, which are mediated through similar mechanisms of oxidative stress and membrane disruption (120). the multifaceted bioactivity of copper

complexes, including their antimicrobial and anti-inflammatory properties, highlights their potential as therapeutic agents in treating infections and inflammatory conditions (122)(20)(123).

Pharmaceutical Applications

Copper complexes have emerged as promising anticancer agents due to their unique mechanisms of action and potential for reduced side effects compared to traditional chemotherapeutics like Cisplatin. Preclinical studies have highlighted several copper-based compounds, such as Casiopeínas® and copper-NSAID complexes, which demonstrate significant cytotoxic activity against cancer cells. Casiopeínas®, a family of mixed chelate copper(II) complexes, have shown antineoplastic potential through mechanisms involving DNA binding, reactive oxygen species (ROS) production, and oxidative damage leading to apoptosis. These complexes have progressed through preclinical trials, with Casiopeína III-ia reaching clinical phase I studies in Mexico (17)(124). Copper-NSAID complexes, such as those incorporating diclofenac, have been designed to target cancer stem cells (CSCs) by elevating intracellular ROS and inhibiting cyclooxygenase-2 (COX-2) activity, which triggers stress pathways and caspase-dependent apoptosis (125). The versatility of copper complexes is further demonstrated by their ability to induce various forms of cell death, including apoptosis, autophagy, and paraptosis, through mechanisms like proteasome inhibition and topoisomerase inhibition (126)(109)(127). Additionally, copper's redox properties facilitate the generation of ROS, which selectively targets cancer cells due to their heightened vulnerability to oxidative stress (17)(128). Despite these promising results, the translation of copper complexes from in vitro to clinical settings has been challenging, often due to issues like copper leaching and speciation in biological fluids (125). Nonetheless, the ongoing development of stable copper complexes with enhanced bioavailability and specificity continues to hold potential for future cancer therapies (129)(130).

Copper complexes have emerged as promising anticancer agents, particularly in overcoming multidrug resistance (MDR) in cancer therapy. These complexes exploit the unique properties of copper, such as its redox activity and ability to form stable complexes with various ligands, to induce cancer cell death through multiple mechanisms. One notable class of copper complexes, di-2-pyridylketone thiosemicarbazones, has demonstrated the ability to overcome P-glycoprotein (P-gp) mediated MDR by forming redox-active complexes in cancer cell lysosomes and upregulating the metastasis suppressor protein NDRG1 (131). Additionally, apoferritin-encapsulated copper complexes (AFt-Cu) have shown efficacy in inducing oncosis in multidrug-resistant colon cancer cells, with certain isomers targeting the nucleus to trigger cell death, thus overcoming MDR in vivo (132). Elesclomol-copper (ES-Cu) nanoparticles have also been developed to bypass P-gp, effectively delivering the copper complex to both drug-sensitive and drug-resistant cancer cell lines, thereby inducing mitochondrial oxidative stress and copper-dependent cell death (cuprotosis) (133). Furthermore, copper complexes have been shown to induce various forms of cell death, including apoptosis, autophagy, and paraptosis, by disrupting cellular copper homeostasis and activating stress pathways (129)(126). The versatility of copper complexes in targeting different cellular mechanisms and their ability to be modified for enhanced delivery and reduced toxicity make them a compelling alternative to traditional platinum-based drugs, which often suffer from severe side effects and resistance issues (134)(135).

Copper complexes have emerged as promising antimicrobial and antiviral agents, particularly against methicillin-resistant Staphylococcus aureus (MRSA), fungi, and emerging viruses. The biocidal properties of copper have been recognized for centuries, with copper ions and complexes being used to disinfect various materials and human tissues due to their potent antibacterial, antifungal, and antiviral activities (136)(137). Recent studies have focused on the development of copper complexes, such as Schiff base complexes, which exhibit significant antimicrobial and antibiofilm activities against MRSA. These complexes, when combined with antibiotics like oxacillin and vancomycin, show additive effects, enhancing their efficacy against both planktonic and biofilm-forming S. aureus strains (138). Additionally, copper(II) complexes with NN2 pincer-type ligands have demonstrated effective inhibition of MRSA and Candida albicans, with mechanisms involving the disruption of cell wall biosynthesis and protein dysfunction (139). The antifungal properties of copper are further supported by its use in copper-impregnated products, which have shown efficacy in reducing fungal infections such as athlete's foot (140)(141). Moreover, copper complexes have been explored for their antiviral capabilities, with applications in antiviral gloves and filters that deactivate viruses like HIV-1, highlighting their potential in addressing viral transmissions and healthcare-associated infections (140)(141). The versatility of copper complexes is also evident in their ability to act as catalysts in various biological systems, further enhancing their antimicrobial and antiviral activities (28). The ongoing research and development of copper complexes underscore their potential as effective agents in combating multidrug-resistant pathogens and emerging viral threats, offering a promising avenue for future clinical applications (142)(143)(144).

Copper complexes have emerged as promising agents in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's, primarily through their role in chelation therapy. Copper is a crucial trace element involved in various biological processes, including neurotransmitter synthesis and protection against oxidative damage. However, its dysregulation is linked to neurodegenerative disorders due to its role in oxidative stress and amyloid-β (Aβ) aggregation, which are hallmarks of Alzheimer's disease (AD) (145)(146). Chelation therapy aims to restore metal homeostasis by using agents that can selectively bind copper ions, thereby preventing their interaction with Aβ and reducing the formation of neurotoxic species and reactive oxygen species (ROS) (147)(148). Clioquinol and PBT2, both based on an 8-hydroxyquinoline scaffold, have been evaluated for their ability to disrupt metal-Aβ interactions and regulate redox homeostasis in AD brains (149). These chelators can cross the blood-brain barrier, a critical feature for effective treatment, and have shown potential in reducing Aβ deposition and associated neurotoxicity in preclinical models (150). Furthermore, novel approaches such as the use of peptoid-based chelators in combination therapies have been proposed to enhance selectivity and efficacy in targeting copper over zinc, which is also present in the synaptic cleft (151). In addition to Alzheimer's, copper chelation is being explored for its neuroprotective effects in Parkinson's disease, where metal ion homeostasis is similarly disrupted (147). The development of copper-binding peptides, such as TP*, which can selectively bind copper without disrupting essential neuroprotective interactions, represents a significant advancement in the design of therapeutic agents for AD (152).

Copper complexes have emerged as promising agents in the management of diabetes and neurodegenerative diseases due to their multifaceted biological activities. These complexes exhibit insulin-mimetic properties, which are crucial for their potential use as anti-diabetic agents. The ability of copper complexes to mimic insulin action is attributed to their role in modulating glucose metabolism and enhancing insulin signaling pathways, similar to other metal complexes like vanadium and zinc, which have been shown to regulate blood glucose levels effectively (153)(154)(155). Specifically, copper complexes have demonstrated significant inhibition of α-glucosidase, an enzyme involved in carbohydrate digestion, thereby reducing postprandial blood glucose levels, which is a critical aspect of diabetes management (156)(157). Furthermore, copper's role in diabetic complications is linked to its involvement in oxidative stress and inflammation, where copper complexes can enhance the activity of superoxide dismutase (SOD), an enzyme that mitigates oxidative damage, thus offering protective effects against diabetes-related tissue damage (158)(159)(18). In the context of neuroprotection, copper complexes have shown potential in modulating copper homeostasis in the brain, which is crucial for preventing neurodegenerative processes associated with diseases like Alzheimer's (18). The therapeutic potential of copper complexes is further supported by their ability to facilitate tissue repair and modulate copper-dependent enzymatic processes, which are vital for maintaining cellular homeostasis and function (158)(160). the diverse pharmacological activities of copper complexes, including their insulin-mimetic and neuroprotective properties, underscore their potential as therapeutic agents in the treatment of diabetes and neurodegenerative diseases, warranting further research and development in this area (156)(158)(18).

Copper complexes have emerged as promising agents in theranostic applications, particularly for combined imaging and therapy in cancer treatment. These complexes leverage the unique properties of copper isotopes and their ability to form stable coordination compounds, which are crucial for both diagnostic imaging and therapeutic interventions. Copper isotopes such as 64Cu and 67Cu are particularly noteworthy; 64Cu is used in positron emission tomography (PET) imaging due to its positron-emitting properties, while 67Cu serves as a β–-emitting radionuclide suitable for targeted therapy (161)(162). The development of copper-based nanoplatforms, such as poly(amidoamine) dendrimer-coordinated copper(II) complexes, has enabled the integration of radiotherapy-enhanced magnetic resonance imaging (MRI) and chemotherapy, providing a synergistic approach to treating tumors and metastases (163). Additionally, copper complexes have been designed to target specific tumor markers, such as the somatostatin receptor 2, using bifunctional chelators like MeCOSar, which enhance tumor-to-background contrast in PET imaging (164). The versatility of copper complexes extends to their ability to induce various forms of cell death, including apoptosis and autophagy, through mechanisms like reactive oxygen species accumulation and proteasome inhibition, making them effective in cancer therapy (165). Furthermore, copper-based nanocomposites have been developed for combined cancer therapies, integrating modalities such as photothermal therapy, chemodynamic therapy, and photodynamic therapy, which enhance the therapeutic efficacy while minimizing side effects (166). The ability to control the redox potential and lipophilicity of copper complexes, as demonstrated with bis(thiosemicarbazone) ligands, further optimizes their use in PET imaging and radiopharmaceutical applications (167). the integration of copper complexes in

theranostic applications represents a significant advancement in precision oncology, offering a multifaceted approach to cancer diagnosis and treatment.

Pharmacokinetics and Toxicity Considerations

Copper complexes present significant challenges in terms of bioavailability and biodistribution, particularly concerning cellular uptake and penetration of the blood-brain barrier (BBB). The lipophilicity of copper complexes is a critical factor influencing their ability to penetrate the BBB, as demonstrated by studies on copper-67 complexes with tetradentate Schiff-base ligands, where increased lipophilicity correlated with enhanced brain uptake, although it was not the sole determinant (168). The design of copper complexes that can effectively cross the BBB is further complicated by the need to balance lipophilicity with other pharmacokinetic properties, such as stability and clearance rates (168). Additionally, the use of human serum albumin (HSA)-cell penetrating peptide conjugates has shown promise in improving the delivery and targeting of copper complexes to brain tumors, suggesting that conjugation with peptides can enhance BBB penetration and therapeutic efficacy (169). The incorporation of amine and polyamine functional groups into copper complexes has also been explored to modify their biodistribution and improve cellular uptake, indicating that structural modifications can significantly impact the pharmacokinetics of these compounds (170). Despite these advancements, the precise mechanisms of copper uptake and trafficking in the brain remain complex, involving interactions with various biological ligands and enzymes, which are crucial for maintaining copper homeostasis and preventing neurotoxicity (171)(172). The therapeutic manipulation of copper bioavailability, particularly in the context of neurodegenerative diseases, underscores the importance of understanding copper's role in brain function and the challenges associated with its pharmacokinetic modulation (173)(172). while significant progress has been made in designing copper complexes with improved BBB penetration, ongoing research is needed to fully elucidate the factors influencing their bioavailability and to develop strategies that optimize their therapeutic potential while minimizing toxicity (174)(175).

Copper metabolism and excretion are intricately regulated processes involving several key proteins, with ceruloplasmin playing a central role. Ceruloplasmin is a multicopper ferroxidase that accounts for over 95% of the copper found in plasma and is crucial for maintaining copper homeostasis by facilitating its transport and metabolism (176)(177). It acts as a primary copper carrier in the blood, delivering copper to various tissues and serving as a scavenger of superoxide, thus protecting against oxidative stress (178). In the liver, copper is incorporated into ceruloplasmin, which is then secreted into the bloodstream, highlighting the liver's pivotal role in copper turnover, including absorption, distribution, and excretion (179)(180). The ATP7B protein in hepatocytes is essential for incorporating copper into ceruloplasmin and for its excretion into bile, a process disrupted in Wilson's disease, leading to copper accumulation and associated pathologies (181)(180). In newborns, copper metabolism is adapted to utilize milk ceruloplasmin as a dietary source, with the mammary gland regulating ceruloplasmin levels in milk, thereby controlling copper absorption in infants (179)(182). This adaptation underscores the importance of ceruloplasmin in early development and the potential consequences of copper imbalance in neonates (182). Additionally, ceruloplasmin's role extends beyond copper transport, as it is involved in iron metabolism and has been implicated in various diseases, including

neurodegenerative and cardiovascular disorders (181)(183). Despite its critical functions, ceruloplasmin does not directly participate in copper excretion, which is primarily managed by ATP7B-mediated biliary excretion (180). Understanding the multifaceted roles of ceruloplasmin and other copper transporters is essential for elucidating copper metabolism and addressing related disorders (10)(183).

Balancing therapeutic efficacy with systemic toxicity, particularly concerning liver and kidney burden, is a critical consideration in the use of copper complexes. Copper oxide nanoparticles (CuO NPs) have been shown to induce significant hepatic and renal toxicity in animal models. Studies on rats have demonstrated that CuO NPs can cause severe necrosis and disorganization of liver and kidney structures, with increased caspase 3 immunoreactivity indicating apoptosis (184)(185). Similarly, copper exposure has been linked to chronic kidney disease (CKD) in humans, with a positive dose-response relationship observed between blood copper levels and CKD prevalence in an elderly Chinese population (186). However, copper's role is complex, as both deficiency and excess can lead to liver fibrosis, particularly in metabolic dysfunction-associated fatty liver disease (MASLD) (187). In contrast, copper chelates have shown potential in reducing the toxic side effects of cisplatin, a common chemotherapy drug, without compromising its anticancer efficacy. These chelates can inhibit neoplastic growth and prevent apoptosis, suggesting a therapeutic advantage over traditional treatments (188). Furthermore, copper(II) gluconate, a nutrient supplement, has been associated with increased levels of serum markers indicative of liver and kidney toxicity, although it does not induce oxidative damage (189). The biodistribution and toxicity of copper nanoparticles compared to cupric ions reveal that while both forms increase copper levels in organs like the liver and kidneys, nanoparticles exhibit delayed peak levels and biopersistence, potentially influencing their toxicological profile (190). the necessity for precision medicine approaches to manage copper homeostasis, tailoring treatments to individual metabolic profiles to mitigate toxicity while harnessing therapeutic benefits (187)(191).

Clinical Prospects and Challenges

Copper complexes have emerged as promising candidates in the realm of anticancer therapeutics, with several compounds currently undergoing clinical trials. These complexes, such as those developed by Eleos, Inc., are being evaluated for their ability to target various cancer types through mechanisms like apoptosis induction, oxidative stress, and inhibition of angiogenesis (192)(193). The clinical success of cisplatin has spurred interest in copper-based drugs due to their selective cytotoxicity towards malignant cells, which is attributed to the hypoxic environment of cancer cells that facilitates the reduction of Cu(II) to Cu(I), leading to pro-apoptotic oxidative stress (193). Notably, two copper complexes have reached clinical trials, marking a significant step towards the development of copper-based anticancer therapeutics (193). Among these, Casiopeína CasIIIia, a mixed chelate copper(II) compound, has entered Phase I trials, demonstrating cytostatic, cytotoxic, and antineoplastic activities in vitro and in vivo. Its mechanism involves DNA interaction and ROS generation, which induce apoptosis in tumor cells (194). Despite their potential, the clinical application of copper complexes faces challenges such as solubility issues and unpredictable mechanisms of action, which have hindered their widespread adoption in clinical therapy (195). However, ongoing research and trials continue to explore their efficacy and safety, with the aim of overcoming these limitations and expanding their use in cancer treatment

(127)(196). The unique properties of copper complexes, including their ability to generate reactive oxygen and nitrogen species, offer alternative mechanisms to traditional anticancer agents like cisplatin, potentially leading to novel therapeutic strategies (197). As research progresses, the development of copper complexes as anticancer agents remains a dynamic and promising field, with the potential to significantly impact cancer therapy in the future (129).

The translation of copper complexes from laboratory research to clinical and industrial applications faces several significant barriers, including scalability of synthesis, regulatory hurdles, and cost-effectiveness. Scalability is a critical challenge, as the synthesis of copper complexes often involves complex coordination chemistry that can be difficult to reproduce on a large scale. For instance, the synthesis of copper (II) complexes with amino acids, which have promising medicinal properties, requires precise control over reaction conditions to maintain their structural integrity and functional adaptability, making large-scale production challenging (198). Additionally, the synthesis of linear copper complex arrays for applications in molecular electronics and light-emitting devices also presents scalability issues due to the intricate coordination and precise arrangement of metal atoms required (199). Regulatory hurdles are another significant barrier, particularly concerning the safety and biocompatibility of copper-based nanomaterials. The potential toxicity of copper nanoparticles necessitates thorough toxicity assessments and biocompatibility studies to meet regulatory standards for clinical use (200). Furthermore, the presence of thiol-rich molecules like glutathione in biological systems poses a challenge for the stability and efficacy of copper complexes, as these molecules can compete with copper ions, potentially leading to dissociation or inactivation of the complexes (201). Cost-effectiveness is also a concern, as the development of copper complexes as therapeutics involves high-throughput chemistry and computer-aided drug design, which can be resource-intensive (202). Despite these challenges, copper complexes hold significant potential as anticancer agents and in other medical applications, with ongoing research focused on overcoming these barriers through innovative synthesis methods and collaborative efforts to ensure their safe and effective integration into clinical practice (127)(109).

The future directions for copper complex nanodelivery systems, particularly involving liposomes and metal-organic frameworks (MOFs), are promising and multifaceted. Copper complexes have shown potential in cancer therapy due to their ability to induce oxidative stress and inhibit proteasome activity, which can be leveraged in nanomedicine for targeted drug delivery and theranostics (203). Liposomes have been effectively used to encapsulate copper complexes, enhancing their delivery and therapeutic efficacy. For instance, a liposomal form of 2-alkylthioimidazolone-based copper complexes demonstrated improved delivery and reduced cytotoxicity in cancer therapy (204). Additionally, the encapsulation of copper-drug complexes like Cu(DDC)2 within liposomes has addressed solubility challenges, enabling the development of new anticancer therapeutics (205). The interaction of copper nanoparticles with liposomes also highlights the potential for stable and efficient drug delivery systems, as liposomes can compete with polymers in binding to nanoparticles, ensuring even distribution and stability (206). On the other hand, MOFs offer a versatile platform for drug delivery due to their porous nature, large surface area, and tunable structures. Cu-based MOFs have been explored for

targeted chemotherapy and chemodynamic therapy, showcasing their potential in treating hepatocellular carcinoma through biorthogonally catalyzed reactions (207). The functionalization of MOFs through surface adsorption and pore encapsulation further enhances their drug delivery capabilities, making them suitable for various biomedical applications (208). As nanotechnology advances, the integration of copper complexes with these nanodelivery systems could lead to more effective and targeted therapies, addressing current limitations such as solubility, stability, and targeted delivery to specific tissues or tumors (209)(210). the development of copper complex nanodelivery systems using liposomes and MOFs is poised to significantly impact cancer treatment and other biomedical applications, offering new avenues for research and clinical translation.

The future directions of copper complex-based therapies in personalized medicine, particularly in the context of biomarker-guided therapy, are promising and multifaceted. Copper complexes have shown significant potential in cancer treatment due to their ability to disrupt copper homeostasis, leading to cytotoxic effects on tumor cells (129)(196). The integration of copper complexes into personalized medicine approaches could be enhanced by leveraging biomarkers to tailor treatments to individual patient profiles. Biomarkers, which include genetic, epigenetic, and proteomic variations, are crucial for predicting disease susceptibility and treatment efficacy, thus enabling more precise and effective therapeutic interventions (211)(212). The development of copper-based nanocomposites further exemplifies the potential for personalized cancer therapies, as these materials can be engineered to combine multiple therapeutic modalities, such as chemotherapy and photothermal therapy, thereby enhancing treatment efficacy and reducing side effects (166). Additionally, the use of copper-lowering therapies for conditions like Alzheimer's disease highlights the broader applicability of copper complexes beyond oncology, suggesting their potential role in treating a variety of diseases through personalized approaches (213). The integration of advanced technologies such as artificial intelligence and digital twins could further refine the application of copper complexes in personalized medicine by enabling the simulation and optimization of treatment plans based on individual patient data (214). However, challenges remain, including the need for more efficient biomarker identification and the development of clinical guidelines to facilitate the integration of these therapies into routine practice (212). the future of copper complex-based therapies in personalized medicine is bright, with ongoing research poised to unlock new therapeutic possibilities and improve patient outcomes across a range of diseases.

Conclusion and Perspectives

Copper-based drug development has seen significant advances, particularly in the field of cancer therapy. Notably, di-2-pyridylketone thiosemicarbazones have been effective in overcoming multidrug resistance (MDR) by forming redox-active complexes that enhance the expression of the metastasis suppressor protein NDRG1 in cancer cells. Additionally, apoferritin-encapsulated copper complexes have shown promise in inducing oncosis in MDR colon cancer cells, effectively targeting the nucleus to trigger cell death. Copper-NSAID complexes, such as those with diclofenac, are designed to elevate intracellular reactive oxygen species (ROS) levels, thereby targeting cancer stem cells and promoting apoptosis . Furthermore, the Casiopeínas® family of copper(II) complexes has demonstrated antineoplastic potential, with some compounds progressing to clinical trials. These

developments highlight the versatility of copper complexes in targeting various cellular mechanisms, making them a compelling alternative to traditional chemotherapeutics, especially in addressing the challenges of drug resistance and side effects associated with conventional treatments.

The development of copper complexes for drug therapy, particularly in cancer treatment, reveals several critical gaps in knowledge. Long-term toxicity remains a significant concern, as the safety profiles of these complexes in prolonged use are not well understood, potentially leading to adverse effects in patients. Additionally, the mechanisms by which cancer cells may develop resistance to copper-based therapies are not fully elucidated, which could limit their effectiveness over time. Furthermore, the pharmacokinetics, including bioavailability and biodistribution of copper complexes, require further investigation to optimize therapeutic outcomes while minimizing toxicity. The precise mechanisms of action, such as interactions with DNA and the generation of reactive oxygen species (ROS), also need to be clarified to enhance the design of these therapeutics. Lastly, challenges related to the regulatory approval and scalability of copper complex synthesis pose barriers to their clinical application, necessitating further research to facilitate their transition from laboratory to clinical settings.

Accelerating the clinical adoption of copper complexes in drug development involves several interdisciplinary strategies. Collaboration between chemists and clinicians is essential to ensure that the synthesized copper complexes are effective and safe for clinical use. Integrating nanotechnology can enhance the delivery and efficacy of these complexes, addressing challenges in clinical applications. Personalized medicine approaches, guided by biomarkers, can tailor treatments to individual patient profiles, improving effectiveness and minimizing side effects. Additionally, thorough regulatory and safety assessments are crucial for meeting standards and facilitating approval. Conducting cost-effectiveness analyses can justify the clinical use of copper complexes, while establishing interdisciplinary research initiatives can foster innovation and expedite the translation from laboratory to clinical practice. These strategies collectively enhance the potential for copper complexes to become viable therapeutic options in cancer treatment and other areas .

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