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REVIEW

Copper Complexes and its Role in Biological Activity

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Copper complexes have garnered substantial attention in diverse fields owing to their multifaceted biological activities. The unique redox properties and coordination versatility of copper enable the design of diverse complexes with tailored functionalities, thereby rendering them crucial in numerous biological applications. This review comprehensively outlines the biological potential of copper complexes, focusing on their applications in medicinal chemistry. Copper complexes have shown tremendous potential in medicinal chemistry as a result of their antioxidant, antiviral, antibacterial, and anticancer actions. This review thoroughly examines recent advancements, mechanisms of action, and potential challenges, while highlighting the significant ability and versatility of copper complexes in diverse biological activities.

Keywords: Metal complex, Anticancer, Antimicrobial, Antiviral, Antioxidant.

INTRODUCTION

The adaptability, malleability, corrosion inhibitory and thermal properties of copper have led to an increase in its invention in the industrial and commercial sectors in recent decades. It is one of the trace nutrient that plays an important role in the activities that occur in living organisms [1] and travels through the bloodstream on the plasma protein ceruloplasin, which serves as a cofactor in various enzymes including oxidase of cytochrome O_2 carrying hemocyanin in addition to the biological electron transport system. Copper also plays a role in antioxidant defense, cellular respiration, iron metabolism, connective tissue formation and neurotransmission [2]. Copper compounds have been studied as prospective therapeutic agents in diagnostic pharmaceuticals and cancer therapy in recent years [3,4]. Coordination compounds of copper have high activity among all the transition metals. They were found to be a potential candidate for DNA binding and DNA condensing probes for gene delivery [5]. In cells, several Cu^{2+} coordination molecules easily interact with glutathione to form adducts, leading to the formation of the Cu(I) coordination molecule. In Fenton-like reaction, this substance has the ability to produce superoxide anion, which can result in ROS production [6]. They have several uses in analytical chemistry, agrochemical industries, catalytic agents, anti-inflammatory agents, fungicides and antiradical agents [7,8]. The antibacterial assessment of copper complexes produced from Schiff base ligands is crucial in protein and enzyme biosynthesis [9]. Numerous compounds containing copper(II) have been studied for their ability to prevent cell division. The enzymatic activity of copper complexes containing nonsteroidal anti-inflammatory medications (NSAIDs) has also been reported [10-12]. Copper is also necessary for the growth of plants and animals, but it can be hazardous to them if its concentration exceed over the amount required for regular functioning. A number of factors, including environmental copper emissions, pH changes and reduction and oxidation potentials, might enhance the bioavailability of copper [13]. This study will primarily focus on the biochemical uses of copper complexes, such as their antibacterial and antifungal properties [14], antitumor and cytotoxic characteristics, anti-inflammatory [15] and antioxidant capabilities.

Applications of copper complexes: Understanding the biological activities of copper complexes is pivotal for harnessing their full potential and advancing their applications in crucial areas of science and medicine.

Cytotoxic and antitumor action: Copper coordinated complexes, owing to the diverse coordination geometries and redox activities of copper ions, have emerged as intriguing candidates for their potential antitumor and cytotoxic activities. These complexes exhibit a range of biological behaviours that can be leveraged for therapeutic purposes. Their ability to generate ROS and induce oxidative stress which contributes to their cytotoxic effects, causing DNA damage and impairing cell viability in cancer cells [16]. These ROS systems are required for maintaining the homeostatic quantity of copper in human bodies. Copper is also thought to be a prophylactic alternative for a variety of carcinogenesis related aspects, including as development, growth and metastasis [17,18]. The usage of numerous targeted anticancer medications of copper can reduce the adverse effects of cancer causing cells while increasing their anticancer efficacy. Copper compounds have a substantial inhibitory effect on topoisomerases [19], which are important in DNA topological regulation. Copper complexes of topoisomerase inhibitors function through many molecular pathways that effect death effectors and cell cycle checkpoints. Alkylating chemicals attach to DNA and cellular proteins and cross-linked DNA strands, limiting DNA replication [20] and RNA transcription [21]. These enzymes of DNA cleaving are categorized into two categories [22] based on their activity: type I (TOPO I), which uses the strand passage mechanism to relax the DNA after cleaving just one strand and type II (TOPO II), which uses the twisting mechanism to relax the DNA after cleaving both strands. Sorting these enzymes into type IA and type IB based on enzyme binding with the phosphate (5′ and 3′) and type IIA and type IIB based on the topological factors is done [23]. Certain antitumor medicines work by either directly binding to DNA or indirectly blocking DNA enzymes such as TOPO [24]. Certain substances change or cleave DNA, impacting the metabolic activities of the cell [25]. Metal complexes have also been identified as possible TOPO inhibitors in a few investigations [26,27]. Few research indicates that complexation, particularly with copper ion, boosts TOPO inhibition activity [28-30].

Aboelmagd *et al.* [31] synthesized a copper complex $[Cu(L^1)_2(H_2O)_2]$ from methyl-3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoic acid and evaluated its anticancer properties. The chemical has the potential to be used as a chemotherapeutic antitumor medication, since it inhibits the growth involving human colorectal carcinoma cells (HCT-116) but not of normal human body cells (HEK-293).

Casiopeinas are the copper compounds prepared by combining ligands (glycinate, phenanthrolein or acetyl acetonate) with 2,2-bipyridine [32]. These compounds have been demonstrated to exhibit significant anticancer action opposed to a wide range of cancer cell types. Copper compounds synthesized from *o*-iodohippuric acid show anticancer action by decreasing the proliferation of lung adenocarcinoma cell growth (by roughly 35%) against A549 cell lines [33] within 24 h when administered at 75 nm concentration, but healthy cells remain unaffected.

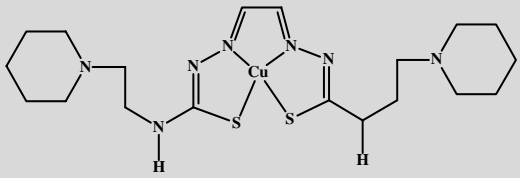
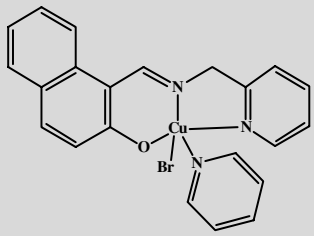
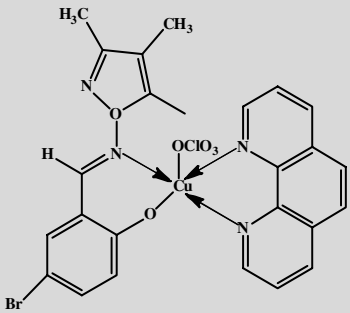
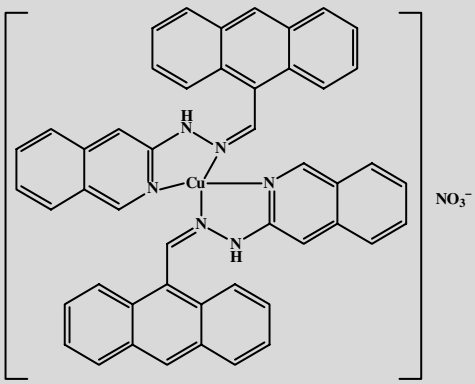
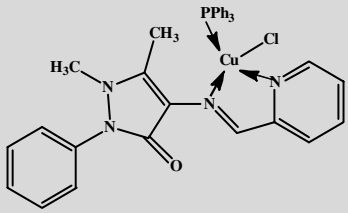
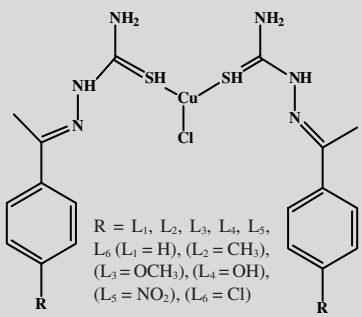
Many signals are required for cell cycle control and signal loss can outcome in cell cycle arrest, reducing cell growth and causing death. Mitosis is the process by which eukaryotic cells divide. When the cell cycle becomes out of control, tumour cells can proliferate. Tumour pathogenesis is inextricably connected to the cell cycle. Many anticancer medicines rely on cell cycle arrest to suppress tumor cell growth. Shimada *et al.* [34] found that dysregulation of copper may cause DNA damage and cell cycle arrest. The interaction of NSC319726 with metal ions, particularly heavy metals, is the cause of cancer cell death. After interacting with other metal ions, only copper ions significantly increased the inhibitory action of this chemical on cancer, according to studies. Inhibitors of copper binding cause ROS to develop and deoxyribosyl purine to be depleted. These findings imply that copper mediated oxidative stress, which stops the cell cycle, has DNA damage as a major side effect. Therefore, a wide range of medications and environmental variables may be responsible for copper dysregulation and metal induced DNA damage [35].

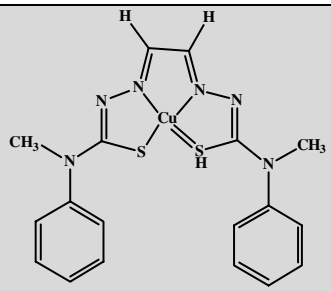
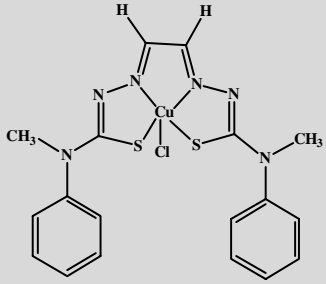
Vanco *et al*. [36] revealed that a new family of hetroleptic compounds containing Cu(II) pomiferin demonstrated significant cytotoxicity and antiproliferative effect against human tumour cells, HOS (osteosarcoma), A2780 (ovarian carcinoma), PC-3 (prostate adenocarcinoma), THP-1 (monocytic leukemia) and Caco-2 (colorectal adenocarcinoma), MCF-7 (breast adenocarcinoma), A549 (lung adenocarcinoma), A2780R (cisplatin resistant ovarian carcinoma). All the synthesized compounds are non-toxic to healthy cells. Iakovidis *et al.* [37] synthesized *bis*-Schiff base complexes that inhibit tumour cell proliferation, delay metastasis and dramatically improve host survival. Role of some copper compounds as antitumor agents is summarized below in Table-1.

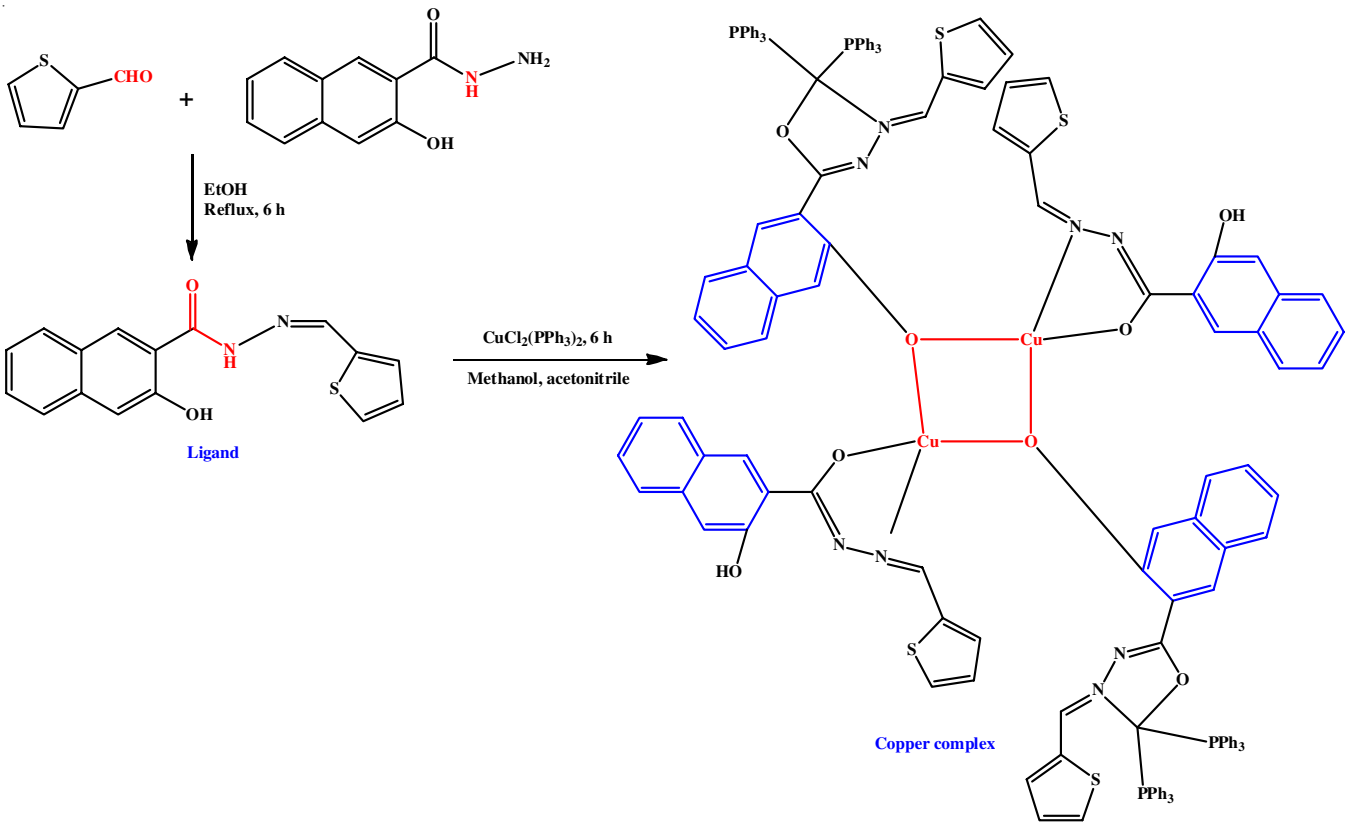
Anu *et al*. [45] synthesized a tetranuclear complex of mixed valence copper(I/II) having ligand (3-hydroxy-naphthalene-2-carboxylic thiophen-2-ylmethylene-hydrazide) (**Scheme-I**). DNA intercalation by metal complex and ligand was measured spectrophotometrically by titrating a calf thymus DNA solution. The binding constants of ligand and complex were found to be $(3.50 \pm 0.73) \times 10^5$ M^{-1} and $(2.34 \pm 0.60) \times 10^5$ M^{-1}, respectively. The fluorescence titration confirms BSA (bovine serum albumin) protein binding.

Krasnovskaya *et al.* [46] synthesized a physiologically active copper coordination compound Cu-ATSM [copper diacetyl-*bis*(N^4-methylthiosemicarbazone)] (**Scheme-II**). The molecule was labelled with the radioactive isotopes ^{60}Cu, ^{62}Cu, ^{64}Cu, employed as a PET hypoxia imaging agent in neck cancer and head [47]. Drug buildup in hypoxic circumstances is linked to Cu(II)/Cu(I) redox changes. Through passive diffusion, radioactively tagged Cu-ATSM entered cells and decreased in glutathione. Intracellular oxygen oxidizes the labile coordination complex Cu^{1+} to the coordination compound Cu^{2+}, which leaves the cell under normoxic circumstances [48]. When exposed to hypoxia, the Cu^+ coordination complex distinguishes into a metal ion and a ligand, which binds to intracellular chaperone proteins and causes a radionuclide to accumulate at hypoxic tumor locations [49]. Since Cu^+ oxidation proceeds too quickly, only hypoxic (tumor) cells exhibit a discernible intracellular drop in Cu(II) ATSM, whereas the medication has no effect on healthy cells [50]. Cu-ATSM was also shown to be a beneficial therapy for enhancing patients' respiratory and cognitive function and

TABLE-1
DETAILS OF SOME COPPER COMPLEXES AS ANTITUMOR AGENTS

Ligand	Type of complex	Coordination mode	Purpose	Ref.
Glyoxal-*bis*(N^4-methylthiosemicarbazonato (GTSM)	CuGTSMpip		Inhibition of cell proliferation in human carcinoma lines PC3.	[38]
2-Naphthalenol,1-(((2-pyridinylmethyl)imino)methyl)	$C_{22}H_{18}BrCuN_3O$		Due to the generation of ROS, the combination is particularly hazardous to A-549 tumor cell lines.	[39]
2-((3,4-Dimethylisoxazol-5-ylimino)meythyl)-4-bromophenol	[Cu(DMIIMBP)-(bipy)ClO_4]		Human cervical carcinoma (HeLa) cancer cells are inhibited in their development.	[40]
9-Quinolylanthra hydrazon	[Cu(9-AQH)$_2$]NO_3		Inhibitory action gainsthuman gastric tumor cell lines (MGC-803)	[41]
5-Dimethyl-2-phenyl-4-[(pyridin-2-ylmethylene)-amino]-1,2-dihydropyrazol-3-one	[CuCl(PPh_3)L]		Inhibits growth of HeLa (cervical tumor cells), MCF-7 (breast tumor) and Hep2 (laryngeal epithelial tumor cells) cell lines	[42]
Bis(thiosemicarbazone)	[Cu(L^{1-6})$_2$Cl]		Kills growth of EAC tumor cells	[43]

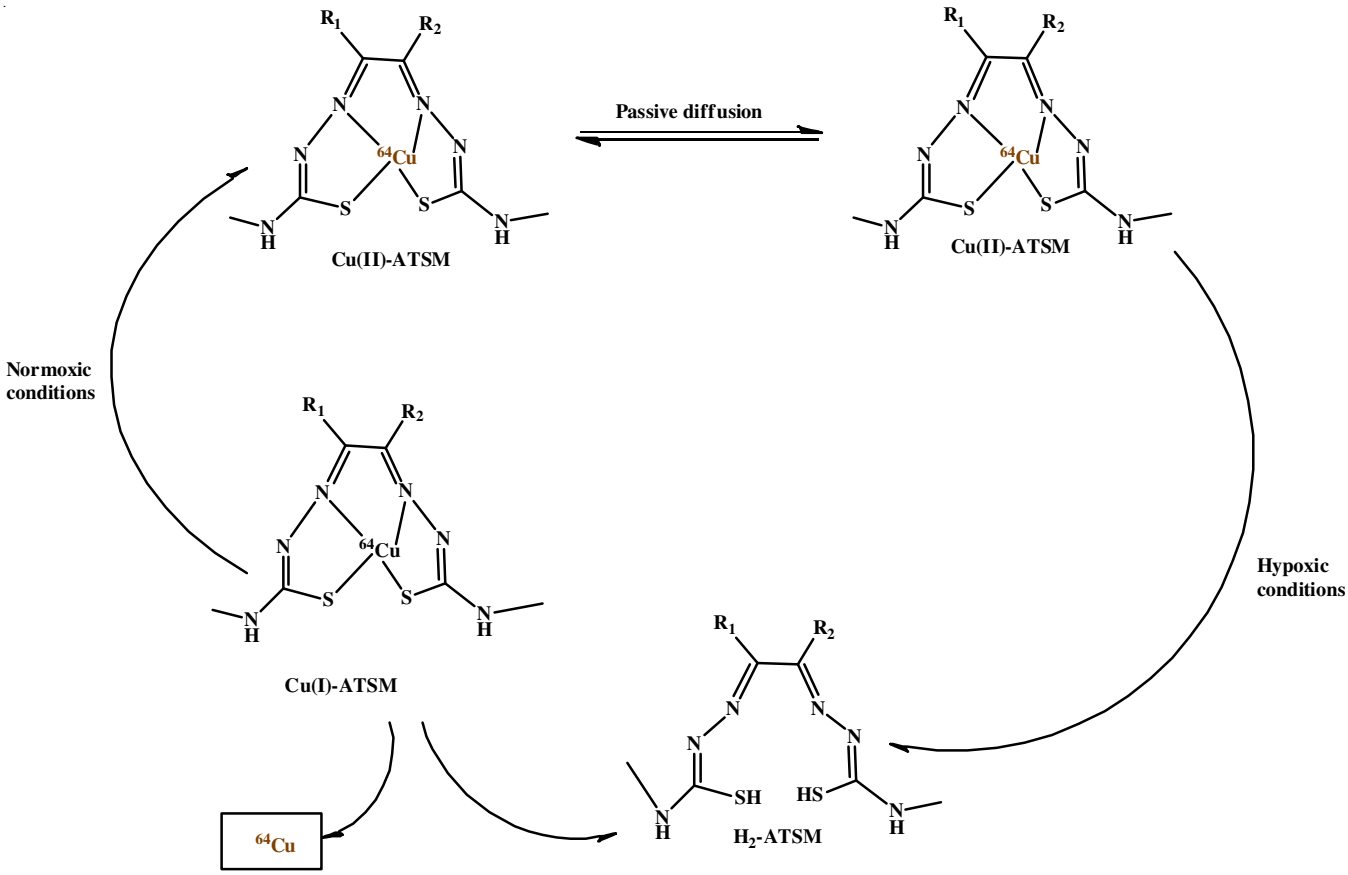
Glyoxal-*bis*(4-methyl-4-phenyl-3-thiosemicarbazone)	[Cu(GTSC)]		Inhibits growth of human cancer cell lines colorectal cancer (HCT-116), breast cancer (MDB-MB-231) & immortalized keratinocyte (HaCat) cells	[44]
	[Cu(GTSCHCl)]			



Scheme-I: Synthesis of ligand (3-hydroxynaphthalene-2-carboxylic thiophen-2-ylmethylene-hydrazide) and corresponding tetranuclear mixed valence copper(I/II) complex [Ref. 45]

also delaying the course of amyotrophic lateral sclerosis. Cu(II)-ATSM is now being tested in clinical studies as a therapy for ALS.

Antimicrobial activities: Copper coordination complexes have gained attention for their notable antimicrobial activities, demonstrating effectiveness against a wide range of microorganisms, including as viruses, fungus and bacteria. The ability of copper complexes to disrupt microbial cell membranes, inhibit vital enzymes and induce oxidative stress plays a significant role in their antimicrobial effects. Their multifaceted mechanisms of action contribute to their effectiveness in fighting against pathogenic microorganisms. Copper ions are capable of damaging the cell membranes, leading to increased permeability and leakage of cellular components, consequently impairing microbial viability. Additionally, these complexes can interfere with crucial cellular processes, affecting enzyme function and leading to the inactivation of essential microbial pathways. Because of their ability to fight drug-resistant strains and their wide-spectrum antibacterial action, copper complexes offer a



Scheme-II: Cellular accumulation of copper diacetyl-*bis*(N^4-methylthiosemicarbazone) [Ref. 46]

viable avenue for the development of novel antimicrobial medicines. Nevertheless, more study is required to completely comprehend their methods of action and enhance their application in combating microbial infections while considering safety and potential toxicity concerns. It has been demonstrated that copper complexes exhibit strong antibacterial properties. Today, a variety of antibiotics are used to combat different types of germs and inhibit the spread of harmful bacteria and fungi that affect human health.

Copper interferes with metabolic activities in *E. coli* cells, causing disruption to the respiratory chain. They also inhibit growth of microorganisms in the living cells. Copper compounds have been shown to selectively inhibit the growth of Gram-positive bacteria. In response to increasing ligand lipophilicity, copper complexes demonstrated higher antibacterial activity. As a result, the current structure activity relationship of basic complexes of copper may give insight into the structural layout of novel coordination complex based antimicrobial drugs. Depending on the complexes structure and the type of ligand, several mechanisms [51,52] of action are conceivable. Since the specific mechanism of copper's antibacterial impact is uncertain, multiple studies have revealed that (ROS) reactive oxygen species formed by Fenton-type reactions [53,54] damage DNA. Copper ion promotes enzyme deactivation, which results in toxicity [55].

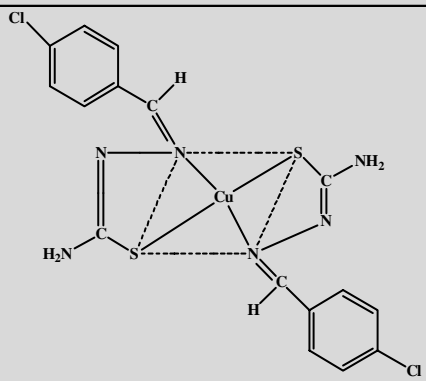
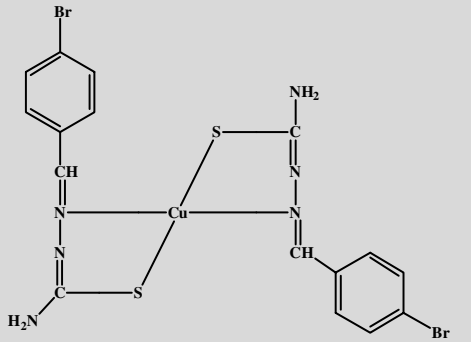
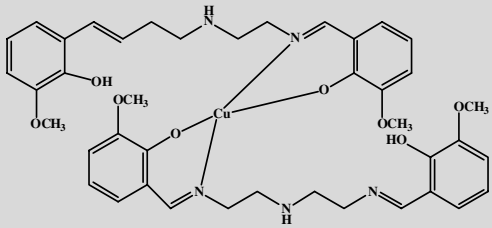
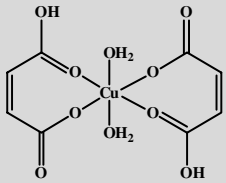
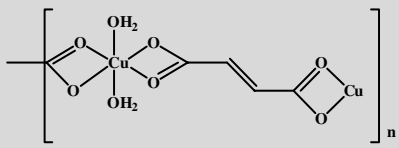
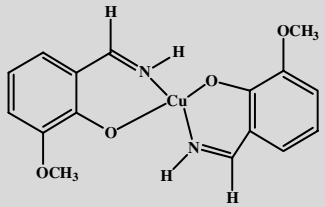
Obaleye *et al.* [56] reported a copper(II) complex having strong antimicrobial activities against *B. subtilis*, *E. coli*, *B. anthrax*, *S. typhi* and fungus *A. niger*. Under the same circumstances, metal complexes are more effective than their equivalent ligands against identical species, which can be explained by chelation theory [57]. Complexes of Cu(II) synthesized from a bidentate Schiff base ligand derived from 2,6-diacetylpyridine were found to be more effective against *E. coli* and other bacteria, but ineffective against *S. aureus* [58]. Copper compounds synthesized from Schiff base containing acetophenone and sulphonamide moieties has also been tested against *B. subtilis* and *E. coli*. In contrast to the free ligand's antibacterial action, the complexes of copper inhibit more [59]. Hazra *et al*. [60] were synthesized two copper(II) complexes with mononuclear pentacoordination with the formula [Cu(L)(Cl)(H_2O)] as well as [Cu(L)(Br)(H_2O)] with HL = (1-[(3-methyl-pyridine-2-ylimino)methyl]naphthalen-2-ol). Copper (II) complexes and their antibacterial activity demonstrated that coordination of Schiff base with a copper metal makes it a better antimicrobial agent than the usual medication chloramphenicol because of bacterial cell penetration *via* chelation. The increased lipophilicity also assists in bacterial cell membrane penetration and restricts germ multiplication.

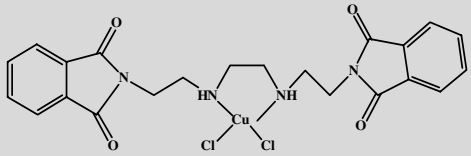
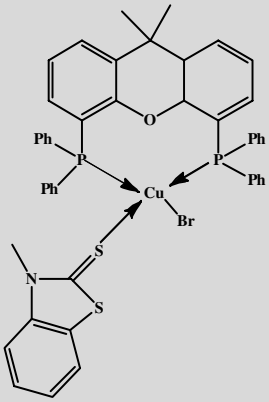
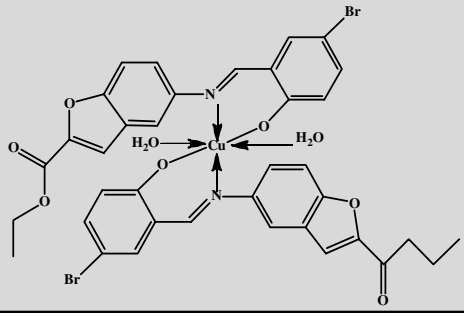
Ajiboye *et al*. [61] synthesized novel copper complex *viz*. copper(II) bis(N-methyl-N-phenyldithiocarbamate), which shows high antibacterial activity against *Salmonella*, *E. coli* and *K. pneumonia*. Prasad *et al*. [62] also synthesized novel mononuclear neutral Cu(II/III) complexes with clomiphene citrate compound, $[M(L)_2(H_2O)_nX_n]$ (where n = 0,1,2...; X = Cl; ½SO_4; CH_3COO; Br), which shows the antifungal efficacy

against the fungus *A. flavus* and *A. niger*. Table-2 shows the role of some copper complexes as antimicrobial agents.

The antimicrobial action of chiral copper(II) with ethylenediamine terpene derivatives were evaluated by Gureva *et al.* [71] and the results indicated that copper complexes (Fig. 1) have strong antibacterial efficacy against methicillin-resistant *S. aureus* strains. Furthermore, these copper complexes have substantially higher antifungal efficacy against *Penicillium notatum*, *Candida albicans* and *Sporobolomyces salmonicolor* strains in comparison to the therapeutic antifungal medication amphotericin [72]. In contrast, the antibacterial activity of free ligands L1-L4 was investigated and revealed that they are inert opposed

TABLE-2
DETAILS OF SOME COPPER COMPLEXES AS ANTIMICROBIAL AGENTS

Ligand	Complex	Structure of complex	Active against microbes	Ref.
para-Chlorobenzaldehyde and thiosemicarbazides	$[CuL_2]$		Significant activity towards *B. subtilis*	[63]
para-Chlorobenzaldehyde and thiosemicarbazides	$[CuL_2]$		*S. aureus* and *B. subtilis*	[64]
6,6'-((1E,1'E)-((azanediyl*bis*-(ethane-2,1-diyl))*bis*-(azanylylidene))(*bis*(methanylylidene))*bis*(2-methoxyphenol))	$[Cu(H_2L)_2]$		*A. baumannii*	[65]
Maleic acid	$[Cu(MA)_2(H_2O)_2]$		*E. coli*, *P. aeruginosa*, *S. aureus* and *B. sereus*	[66]
	$[Cu(MA)_2(H_2O)_2]_n$			
o-Vanillin and 2-methoxyaniline	$[Cu(ovan\text{-}NH)_2]$		*E. coli*, *S. aureus* and *B. subtils*	[67]

2-(-(2-(2-(2-(1,3-Dioxoisoindoline-2-yl-ethylamino)ethylamino)ethyl)isoindoline-1,3-dione (DEEI)	[Cu(DEEI)]		*P. aeruginosa*, *S. enterica*, *S. pneumoniae*, *E. faecalis*, *K. pneumonia* and *E. coli*	[68]
Xantphos	[CuBr(xantphos)]		*E. coli*, *X. campestris*, *B. subtilis* and *B. cereus*	[69]
(E)-Ethyl5-(5-chloro-2-hydroxybenzylideneamino)-benzofuran-2-carboxylate	[$CuC_{18}H_{14}ClNO_4$]		*E. coli*, *S. aureus* and *B. subtilis*	[70]

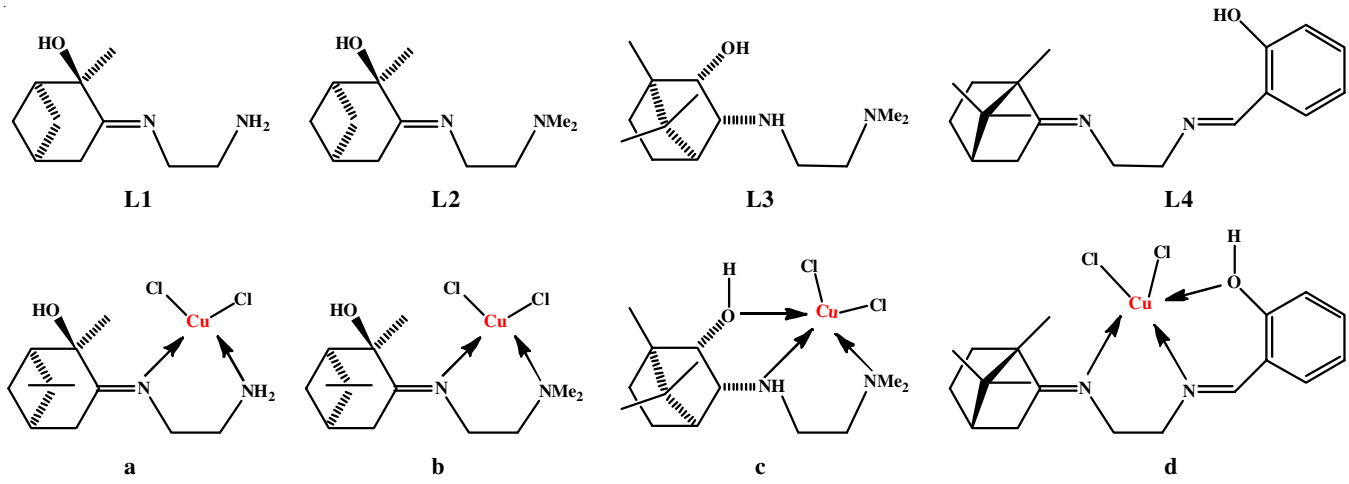


Fig. 1. Structure of ligands and their copper complexes [Ref. 71]

to the pathogenic microorganisms tested. The findings support prior research suggesting free ligands have lesser antibacterial activity than metal complexes. The reason is attributed due to the coordination of the organic ligand, which increases the lipophilicity of Cu^{2+} ions [73-76]. Since the penetration of a large enzymatic co-factor, the metal becomes potentially toxic to bacteria and fungus, particularly unicellular bacteria.

Ejidike & Ajibade [77] synthesized Co(II), Ni(II), Cu(II) and Zn(II) complexes with (4*E*)-4-[(2-{*E*-[1-(2,4-dihydroxyphenyl)ethylidene]amino}ethyl)imino]pentan-2-one as ligand and evaluated against antimicrobial activity. Since copper(II) complex had a better ability to coordinate with the ligand in the order H_2L < Zn(II) < Ni(II) < Co(II) < Cu(II) than all other metal complexes, it showed lower to higher activity against Gram-positive bacteria; *S. faecalis* (ATCC 29212), *S. aureus* (ATCC 25923) and *B. cereus* (ATCC 10702) as well as Gram-negative bacteria; *S. flexneri* (KZN), *P. aeruginosa* (ATCC 19582) and *E. coli* (ATCC 25922). The pathogen cell membrane and the nature of metal atom are responsible for this variation in the antibacterial activity. Moreover, these complexes outperform ligands as bactericidal agents supporting the Tweedy's chelation hypothesis.

The mechanism of coordination compounds and their action in regard to the bacterial chromosome, results in a reduction in bacterial reproduction. Copper ion redox activity is affected by the existence of reducing agents. In the majority of Gram-positive bacteria, the reducing agent is bacillithiol [78]; however, in certain Gram-negative bacteria, it is glutathione. Copper induced DNA damage can kill bacteria regardless of their physiological condition or growth rate. Under some circumstances, biofilms protect microorganisms and improve their adaptability to the external environment. Biofilms have the potential to influence both the immune system and the effectiveness of antibiotics, thereby fostering antibiotic resistance and facilitating the development of chronic or persistent illnesses. Although less active on planktonic cells than vancomycin [79], they are significantly more active on biofilms. As a result of their method of action, copper coordination compounds are more effective than standard antibiotic therapy and have an effective synthetic antibacterial agents.

Anti-inflammatory and antioxidant properties: Copper coordination complexes have exhibited promising antioxidant and anti-inflammatory properties, exhibiting their potential in mitigating oxidative stress and inflammatory responses within the biological systems. These complexes, through their redox-active nature, exhibit the capacity to scavenge ROS, minimizing oxidative damage in tissues and cells. This antioxidant activity contributes to their potential in alleviating oxidative stress related conditions. Copper complexes also regulate the synthesis of pro-inflammatory mediators and modulate many inflammatory pathways, which leads to their anti-inflammatory effects. They have been observed to stop the activity of certain enzymes involved in inflammatory processes and suppress the production of inflammatory cytokines, ultimately contributing to the attenuation of inflammation. While these properties hold promise for potential therapeutic applications, the complex interplay between copper and biological systems necessitates a thorough understanding of their behaviour to harness their benefits effectively, ensuring both efficacy and safety in clinical or biomedical applications.

Nonsteroidal anti-inflammatory medications (NSAIDs) [80] are analgesics, anti-inflammatory and antipyretic drugs, which are frequently used to relieve fever and pain. Complex formation with O- and N- as donor groups can significantly improve the characteristics of NSAID compounds since these groups encourage metal coordination.

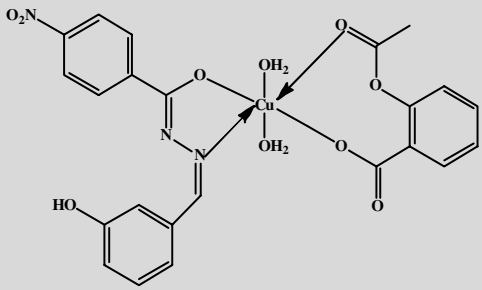
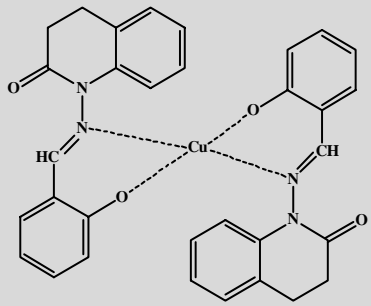
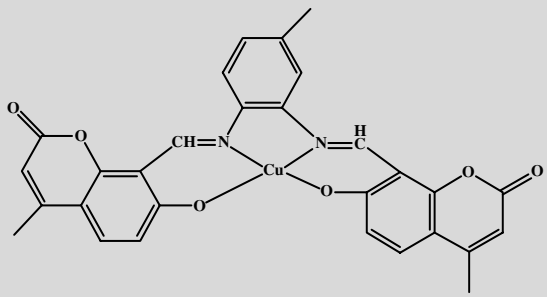
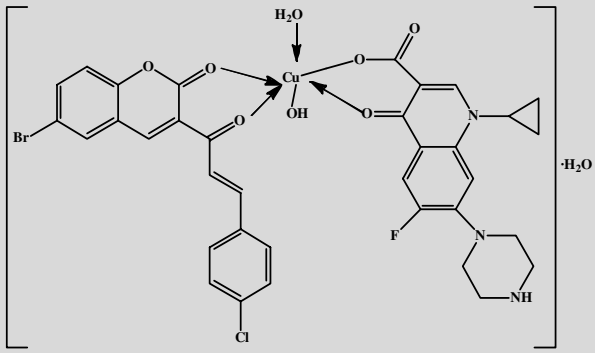
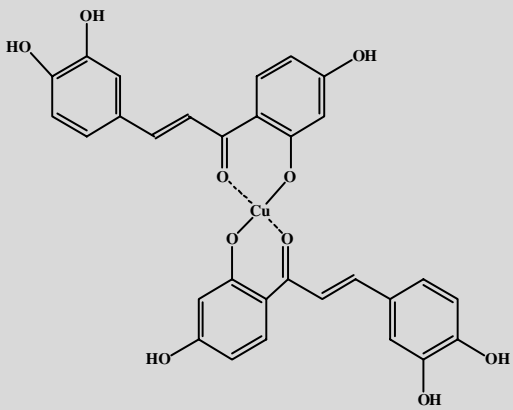
Chemical compounds known as antioxidants protect human cells from the free radical damage and serve an important function in avoiding damage to macromolecules and cells in living organisms by halting or controlling the oxidation of reactive species [81,82]. Cancer, liver damage, cardiac arrest, diabetes and other disorders are caused by free radicals [83]. These antioxidants have the capacity to scavenge and protect our bodies against illnesses induced by them [84]. Antioxidants can also operate as catalysts in industry as anticorrosion agents and also in antifungal, anti-inflammatory, antibacterial and antiviral medicines [85]. ROS generated by metabolic activities in the human body, which include superoxide anion, hydrogen peroxide and hydroxyl radical, are widely known as highly reactive and possibly harmful transitory chemical entities. The ROS induced oxidative damage to proteins, lipids and nucleic acids has been related to a number of chronic disorders such as atherosclerosis, cancer, ageing and coronary heart disease [86]. As a result, it is vital to offer antioxidant-rich drugs in order to avoid free radical damage in the body. The antioxidant defense system works on three levels: (i) inhibit free radical formation (*e.g.* transition group metal ion-binding proteins and antioxidant enzymes); (ii) preventing free radical formation and (iii) preventing the development of free radicals. The complexity of the processes and their working environment causes antioxidants, which are hydrophilic and lipophilic, to display a wide variety of molecular shapes and sizes.

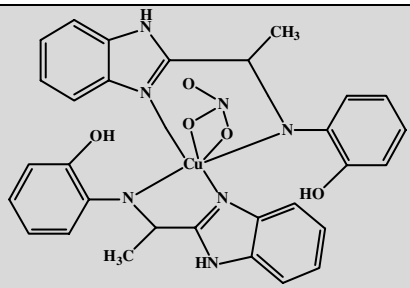
Fountoulaki *et al.* [87] have synthesized $[Cu(difl)_2(py)_2]$ and $[Cu_2(difl)_4(DMF)_2]$ complexes containing NSAID medication diflunisal. These complexes have substantial DNA binding capacity with bovine and human albumin proteins, as well as a high binding constant. The affinity of the diflunisal molecule for both proteins increases when linked with copper metal. Malis *et al.* [88] formed six copper(II) compounds with diverse medicines as ligands, including ibuprofen, loxoprofen, fenoprofen and clonixin. Complexes $[Cu(ibu)_2(py)_2(H_2O)]$ and $[Cu(clon)_2(neoc)]$ exhibit the exceptional activity against H_2O_2 reduction, whereas complex $[Cu_2(feno)_4(DMF)_2]$ has a good capacity to successfully scavenge the radicals DPPH and ABTS. Another new copper complex $[CuL_2(yl)phenol]$ synthesized by Aiyelabola *et al.* [89] shows strong inflammatory properties. This complex efficiently blocks or postpones lysosomal membrane lyses. Similarly, Vadivel *et al.* [90] synthesized a copper complex $[Cu(cxb)_2Cl_2]$ using celecoxib as ligand. They tested it against the receptor cyclooxygenase II and results verified that the synthesized complex inhibited more effectively than free ligand. Similarly, the Cu(II) complexes containing pomiferin [36] can be employed as anti-inflammatory drugs by suppressing inflammation related signaling pathways (NF-κB translocation, TNF-α secretion and NF-κB/AP-1 activity).

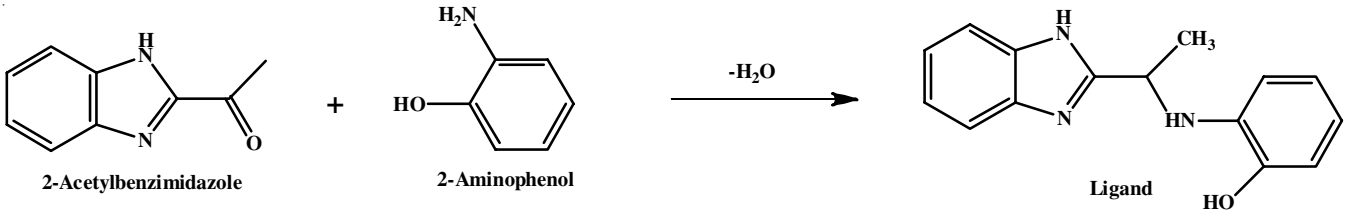
Horozic *et al*. [91] synthesized a new copper (II) complex from tryptophan and 2,2-dihydroxyindane-1,3-dione as ligands. This complex has lesser antioxidant activity than vitamin C but higher than ligand. Using mixed Schiff base ligands, recently, Ashrafuzzaman *et al.* [92] synthesized a copper(II) complex, whose antioxidant properties are found to be ptent than that of the free ligand. The antioxidant activity exhibited by several copper complexes are summarized in Table-3.

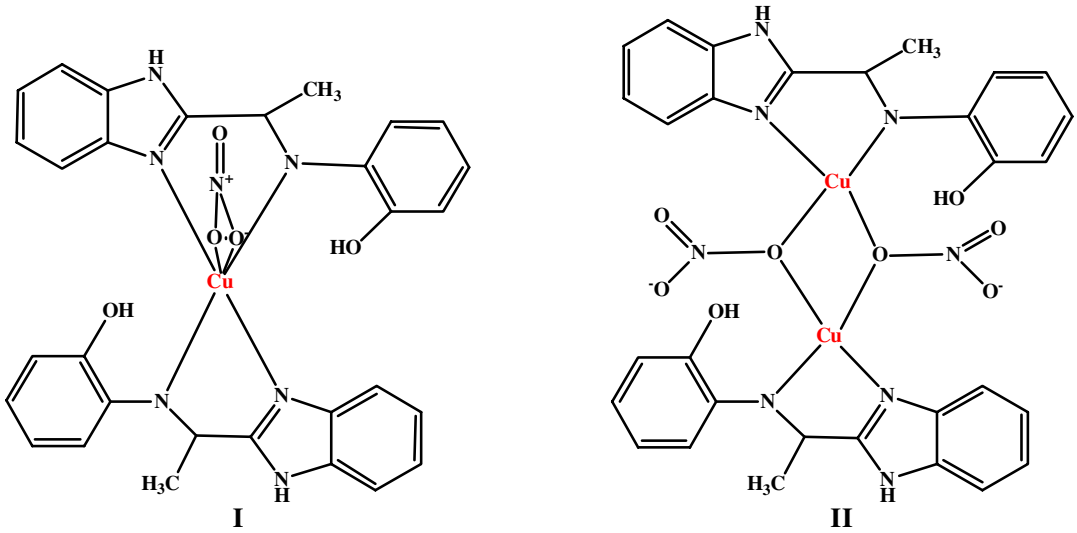
Hu *et al*. [99] synthesized two mononuclear and binuclear copper complexes $[CuL_2NO_3]NO_3{\cdot}2C_2H_5OH$ and $[CuL_2NO_3]_2{\cdot}2C_2H_5OH]$ containing *N*-(methyl-2-benzimidazolmethylidene)-2-hydroxyanaline as ligand, respectively (**Scheme-III**). The antioxidant activity of synthesized compounds was analyzed by using hydroxide and superoxide free radical scavenging capabilities. According to the results, complex I is more potent than complex II, however, both complexes are more powerful than the ligand. The inhibitory effects of ligand and complexes have been compared on the basis of O_2^- and $^{\bullet}OH$. This is the impact of the examined compounds on O_2^- and in the studied concentration range, OH increases with concentration and the suppression ratio rises with the sample concentration. The

TABLE-3
DETAILS OF SOME COPPER COMPLEXES AS ANTIOXIDANT AGENT

Ligand	Stoichiometric formula	Structure of complex	Ref.
Aspirin	$[Cu(ASA)(AROY)(H_2O)_2]$		[93]
N-(4-Phenylthiazol-2-yl)-2-(thiophene-2-ylmethylene) hydrazinecarboxamide	$[Cu(L_2)]$		[94]
4-Methyl-7-hydroxy-8-formyl coumarin	[Cu(L)]		[95]
6-Bromo-3-(3-(4-chlorophenyl)-acryloyl)-2*H*-chromen-2-one and ciprofloxacin	$[Cu(L)]\cdot H_2O$		[96]
Polyhydroxychalcone	$[Cu(ISO)_2]$		[97]

N-(Methyl-2-benzimidazol-methylidene)-2-hydroxyanaline	$[CuL_2NO_3]NO_3{\cdot}2C_2H_5OH$		[98]





Scheme-III: Synthesis of copper complex **I**, **II** and ligand [Ref. 99]

inhibitory concentration (IC_{50}) values of ligand, complexes I and II against O_2^- were 4.34, 1.46, and 1.90 M, respectively, indicating that these compounds have stronger superoxide dismutase activity than typical antioxidants like vitamin C (IC_{50}: 852 mM) [100]. The IC_{50} values for the inhibitory effects of these compounds on •OH were 7.36, 3.50 and 4.37 M, respectively. The complexes have stronger antioxidant activity than the ligand andcomplex I has a greater antioxidant property than complex II, which is most likely due to the chelating ability of organic molecules to copper ions [101].

Conclusion

The biological potential of copper complexes, as evidenced by an array of studies and applications across various scientific domains, underscores their significance in contemporary research. The synthesis and utilization of copper complexes have demonstrated remarkable versatility, exhibiting promising biological activities in medicinal chemistry. In conclusion, the multifaceted nature of copper complexes, attributed to their diverse coordination geometries, redox properties and structural variability, offers an extensive spectrum of applications. In medicinal chemistry, the antimicrobial, antiviral and anticancer activities of copper complexes present exciting opportunities for drug development. Despite their potential, development and optimization require addressing critical concerns, such as their stability, potential toxicity and the need for improved selectivity in targeting specific biological pathways. Future research in this area should focus on addressing these challenges to maximize the beneficial effects of copper complexes while mitigating potential drawbacks. Advancements in the field of copper complexes hold significant promise for the advances in therapeutic agents.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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