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Review Article

Biological properties of metal complexes of curcumin

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Abstract

Curcumin, a naturally occurring phenolic compound isolated from *Curcuma longa*, has different pharmacological effects, including antiinflammatory, antimicrobial, antioxidant, and anticancer properties. However, curcumin has been found to have a limited bioavailability because of its hydrophobic nature, low-intestinal absorption, and rapid metabolism. Therefore, there is a need for enhancing the bioavailability and its solubility in water in order to increase the pharmacological effects of this bioactive compound. One strategy is curcumin complexation with transition metals to circumvent the abovementioned problems. Curcumin can undergo chelation with various metal ions to form metallo-complexes of curcumin, which may show greater effects as compared with curcumin alone. Promising results with metal curcumin complexes have been observed with regard to antioxidant, anticancer, and antimicrobial activity, as well as in treatment of Alzheimer's disease. The present review provides a concise summary of the characterization and biological properties of curcumin-metal complexes. © 2019 BioFactors, 00(00):1–14, 2019

Keywords: *curcuminoids; metal; complex; chelation*

Abbreviations: AD, Alzheimer's disease; DPBA, 2-Aminoethyl diphenyl borate; FDA, Food and drug administration; FHV, Flock house virus; FIPV, Feline infectious peritonitis virus; Hb, Hemoglobin; HSV, Herpes simplex virus; IAV, Influenza type A virus; ICAM-1, Intercellular adhesion molecule-1; MCP-1, Macrophage chemoattractant protein-1; MM, Multiple myeloma; NFT, Neurofibrillary tangles; NF-κB, Nuclear factor κB; PIV-3, Parainfluenza virus type 3; ROS, Reactive oxygen species; RSV, Respiratory syncytial virus; SOD, Superoxide dismutase; THBS-4, Thrombospondin-4; VSV, Vesicular stomatitis virus

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1. Introduction

A metal complex is an atom or ion bonded to a surrounding array of molecules or anions that are known as ligands or complexing agents [1]. In recent decades, metal complexes based on natural products are increasing as pharmaceuticals for use as diagnostic agents or as chemotherapeutic drugs. There have been numerous reports on their applications in biology, which include antimicrobial, anticancer, antioxidant, anti-inflammatory, and antiarthritic/antirheumatic activity, as well as exerting positive effects in the treatment of Alzheimer's disease [2]. The interaction of metals with ligands results in drastic changes in the biological effects of the ligand, which include improving the efficacy and/or reducing the negative side effects of the drug molecules (ligands) that are complexed to the metals [3]. Also, transition metals, like copper, iron, and manganese, can interact with active sites of enzymes, playing important roles in multiple biological processes [4]. Cisplatin, carboplatin, and

oxaliplatin are perhaps the best known examples of metal-based drugs [5]. However, approved drugs for the treatment of cancer are usually limited by potential undesirable side effects such as hepatotoxicity, nephrotoxicity, ototoxicity, reduction in platelet counts, and myelosuppression [6]. Curcumin, a natural polyphenolic compound and the principal coloring agent found in the rhizomes of *Curcuma longa* (Zingiberaceae), has several health benefits, including antioxidant [7], anti-inflammatory [8], immunomodulatory [9], antiarthritic [10,11], antithrombotic [12,13], pulmonoprotective [14,15], lipid-modifying [16], neuroprotective [17], anticancer [18,19], antidiabetic, [20,21] and hepatoprotective [22,23] properties. Numerous reports have indicated that curcumin is quite safe and nontoxic to humans up to doses of 12 g/day [24]. Despite curcumin possessing a wide variety of biological activities, a major obstacle to the clinical use of curcumin is related to its reduced bioavailability, because of its hydrophobic nature, low-intestinal absorption, and rapid metabolism [25]. Therefore, there is a need for enhancing the bioavailability and its solubility in water in order to increase the pharmacological effects of this bioactive compound. Alongside the use of nanoparticles, liposomes, micelles, and phospholipid complexes to better improve the bioavailability of curcumin, curcumin complexation with transition metal ions represents yet another approach to circumvent the challenges mentioned above. In one study, it was found that a curcumin–Zn^{2+} complex improved the solubility, stability, and the pharmacodynamic effects of curcumin [26]. Because of the highly conjugated ß-diketone moiety in the chemical structure of curcumin, it can readily form metal chelates of type 1:1 and 1:2 with various metal ions with divalent and trivalent inorganic molecules like Mn^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Al^{3+}, and Fe^{3+}. This results in the formation of metallocomplexes of curcumin, which may show greater effects as compared to free curcumin [26]. Recent reports have demonstrated that the biochemical activities of curcumin are enhanced by metallocomplexes of curcumin [27]. In addition, over the past ten years, complexation of curcumin with several metals has gained much interest as one of the most useful approaches for the evaluation of many of the biological properties of curcumin, such as its anticancer, antioxidant, antimicrobial, and anti-inflammatory activities [28].

2. Antioxidant activity

Many authors have found that antioxidant activity is enhanced by metallocomplexes of bioactive compounds. For example, the antioxidant activity of some flavonoid complexes including quercetin, rutin, catechin, and galangin with Cu^{2+}, Fe^{2+}, Al^{3+}, and Zn^{2+} were tested. It was found that the metals significantly changed the chemical properties of the flavonoids, because the antioxidant activities of the flavonoid complexes were much more effective than the free flavonoids. They suggested that the higher antioxidant activity of the complexes might be explained by the acquisition of additional superoxide dismutating centers [29]. The free radical reaction centers of curcumin may be due to the presence of two phenolic groups, the enol form of the diketone moiety, and the extended conjugated structure [30]. Barik et al. [31] have shown that the antioxidant activity of curcumin in the β-keto-enol form is higher than those in the β-diketone form. There are three factors that influence the antioxidant activity of curcumin: the redox state of the biological environment, the presence of metal ions, and substituents on the side chain [32]. Mohammadi et al. have investigated the antioxidant activity of some complexes of curcumin and its derivatives (diacetylbisdemethoxycurcumin, diacetylcurcumin, demethoxycurcumin, and bisdemethoxycurcumin) when complexed with In^{3+}, Ga^{3+}, and VO^{2+}. These authors have confirmed that the free aromatic ring hydroxyl groups are necessary for conferring the high antioxidant properties of the complexes just mentioned [33]. The antioxidant activity of curcumin and metal complexes formed with Mn^{2+}, Mg^{2+}, Cu^{2+}, Ni^{2+}, and Co^{2+} was evaluated by Priya et al. [30]. They have shown that the curcumin metal complexes have comparable antioxidant activity to the free curcumin. In another study, several divalent metals, including Cu^{2+}, Fe^{2+}, Mn^{2+}, Mg^{2+}, B^{2+}, Se^{2+}, and Zn^{2+}, were chosen to form complexes with curcumin in order to evaluate their antioxidant activity [34]. Their results showed that metal complexed curcumin had better DPPH radical scavenging and ferrous reducing power activities compared to free curcumin. Curcumin-Zn^{2+} was the best metal complex for enhancing the antioxidant activity of curcumin. Low toxicity and few side effects are of the main advantages of using either Zn^{2+} or Cu^{2+} as coordination complexes [35]. Zinc prevents lipid peroxidation and thus plays an essential role in protecting the cells from oxidative stress [36]. In addition, it was reported that metal chelation of curcumin with Fe^{2+}, Mn^{2+}, and Zn^{2+} enhanced the antioxidant activity of curcumin [37]. Superoxide dismutase (SOD) is one of the important enzymes for scavenging reactive oxygen species (ROS) by converting the superoxide into less-toxic hydrogen peroxide and oxygen [38]. In this context, curcumin complexed with Cu^{2+} resulted in a six- and ten-fold increase in lipid peroxidation and SOD activity, respectively [31]. Since curcumin can form both 1:1 and 1:2 complexes with Cu^{2+}, some 1:1 and 1:2 complexes of Cu^{2+} and curcumin were synthesized, and their SOD and antioxidant activities were investigated. The results showed that the 1:1 complex is approximately ten times more active as an SOD mimic and seven times greater than the 1:2 complex in terms of the rate constant for scavenging superoxide radicals. In addition, the 1:1 Cu^{2+}-curcumin complex exhibited more inhibition of lipid peroxidation compared to the 1:2 Cu^{2+}-curcumin complex. These authors have suggested that the low-antioxidant activity of 1:2 Cu^{2+}-curcumin complex is likely due to the rigid structure, which could not undergo the molecular distortions from a square planar geometry when compared to the 1:1 Cu^{2+}-curcumin complex [39]. Vajragupta et al. [40] have also synthesized three manganese stable complexes of curcumin and tested them for lipid peroxidation and SOD activity. All complexes protected the brain with regard to lipid peroxidation, which was comparable to curcumin, while also demonstrating much greater SOD activity than curcumin alone. Gorgannezhad et al. have shown higher DPPH radical scavenging

activity of curcumin when compared to a curcumin-Mn^{2+} complex. These authors have justified this activity by means of lower BDE and higher HOMO and LUMO energy values of curcumin as compared with those of the curcumin-Mn^{2+} complex [41].

3. Alzheimer's disease

Alzheimer's disease (AD), as a multifactorial neurodegenerative disease, is expected to rise to 106.8 million people by 2050. Deposition of extracellular amyloid plaques containing β-amyloid (Aβ) peptide and accumulation of intracellular neurofibrillary tangles (NFT) composed of the hyperphosphorylated tau protein are the pathological hallmarks of AD [42]. Currently, there are no effective treatments available for preventing or delaying the progression of AD. Therefore, the development of a new effective treatment for AD is one of the major challenges in modern medicine, which is urgently needed. The reduction of Aβ oligomer levels and oxidative stress would appear to represent the primary promising targets for the treatment of AD. It is worthwhile to consider the potential effects of curcumin in AD, because of its potent anti-inflammatory and antioxidant activities. At this point in time, there have been numerous in vitro and in vivo studies that have shown the antiamyloid activity of curcumin [42–44]. In fact, the hydrophobic properties of curcumin enable it to cross the blood–brain-barrier and bind to the nonpolar regions of the Aβ oligomers via hydrophobic interactions, which results in blocking the aggregation of Aβ, inhibiting plaque formation, and lowering Aβ oligomer toxicity [24]. Oxidative stress has been reported as one of the main pathognomonic features of AD. Numerous studies have demonstrated the presence of lipid, protein, and nucleic acid oxidation products in the harvested brains of those afflicted with AD [45]. Therefore, a therapeutic strategy that aimed at either removal of free radicals or prevention of their formation might be an alternative approach for slowing the progression of AD. It is well known that the high levels of some metal ions, like Fe^{3+}, Cu^{2+}, Al^{3+}, Zn^{2+}, Hg^{2+}, Mn^{2+} in the brain, play an important role in the pathogenesis of AD. in vitro experiments showed that these metals are able to bind with high affinity to the N-terminus, metal-binding sites in Aβ peptides. Therefore, this process can promote Aβ aggregation, the formation of neurotoxic oligomers, and the induction of oxidative stress through ROS generation, which leads to neuronal cell death [46–48]. The failure of three well-known metal chelators including desferrioxamine, clioquinol, and 8-hydroxyquinoline derivative (PBT2) in clinical studies has prompted the search for alternative agents that can bind (chelate) metals in the brain. The failure of the three metal chelators mentioned above to decrease metal-induced aggregation of Aβ stems from their poor target specificity [46]. The metal-chelating potential of curcumin to bind to several metal ions to form stable complexes could be a possible strategy for the protection of the brain from AD. Curcumin, as a metal chelator, can compete with the peptide for complexation with metals, which would theoretically lead to an inhibition in the formation of peptide-metal complexes that generate ROS and subsequently promote the formation of neurofibrillary tangles and the aggregation of Aβ [49]. Kochi et al. have shown that Gd-cur (a derivative of curcumin that contains gadolinium; Gd^{3+}) could modulate Cu^{2+}-triggered Aβ aggregation more than metal-free or Zn^{2+}-induced analogs [50]. Complexation of curcumin with Cu^{2+} was evaluated in the presence and absence of two different segments of the Aβ protein including the Cu^{2+}-binding (Aβ6–14) and curcumin-binding (Aβ14–23) domains. It was found that curcumin can simultaneously bind to Cu^{2+} and Aβ and, thus, can function both as a chelator and an Aβ binding partner [51]. Drago et al. have compared the effects of β-amyloid and its metal complexes with Al, Zn, Cu, and Fe in human neuroblastoma cells. Binding of Al^{3+} to the Aβ peptide led to the formation of more hydrophobic structures, which resulted in the promotion of Aβ peptide aggregation compared to other metals that were tested [52]. In addition, prolonged Al^{3+} exposure induces oxidative stress and increases the formation of Aβ peptide [53]. Curcumin has a protective effect against Al toxicity due to its strong interaction with Al^{3+}, which would limit the interaction of Al^{3+} with the Aβ peptide [54]. The strong interaction of curcumin derivatives with some other toxic metal ions, like Al^{3+}, Cu^{2+}, and Hg^{2+}, has also been reported [55]. Additionally, the lipophilic Ga^{3+} schiff base-curcumin complex has been found to bind with amyloid-β plaques in human brain tissue. This complex could also be a useful candidate for use as an imaging agent for AD [56]. Banerjee [49] has evaluated the impact of curcumin on Cu^{2+}- and Zn^{2+}-induced oligomerization and protofibrillization of the Aβ peptide and showed that curcumin significantly reduced the β-sheet content of the peptide. Furthermore, he observed that spontaneous fibrillization of the peptide occurs in the presence of Cu^{2+} and Zn^{2+} but is hindered when the peptide is incubated with curcumin, which indicates the beneficial role of curcumin in hindering the aggregation of the Aβ peptide. Several imidazole-containing curcumin analogues were synthesized and evaluated for their role as an inhibitor that could attenuate crosslinking of Aβ induced by Cu^{2+}. The results showed that CRANAD-17, a curcumin scaffold, reduced Aβ fibril formation, inhibited the aggregation of Aβ42, and prevented the β42 cross-linking induced by Cu^{2+} [57]. Likewise, in vivo studies of the metal complex of curcumin with Fe^{3+} have demonstrated a reduction in the accumulation of $Aβ_{25-35}$ and strengthened the memory of rats compared to a curcumin-Mn^{2+} complex and curcumin alone [58] (Fig. 1).

4. Anticancer activity

Over the last decades, several metal complexes have been widely evaluated in vitro and in vivo for their anticancer activity. Most anticancer metal-containing compounds include organic ligands that often contain planar aromatic ring systems. When these organic ligands are bound to the central metal atom through direct carbon-to-metal bonds, the resulting compounds are defined as organometallic [59]. There are several organometallic anticancer agents that are complexed with platinum (PtII and PtIV), ruthenium (RuII and RuIII), gold (AuI and AuIII), and titanium (TiIV), which are currently being evaluated in clinical trials

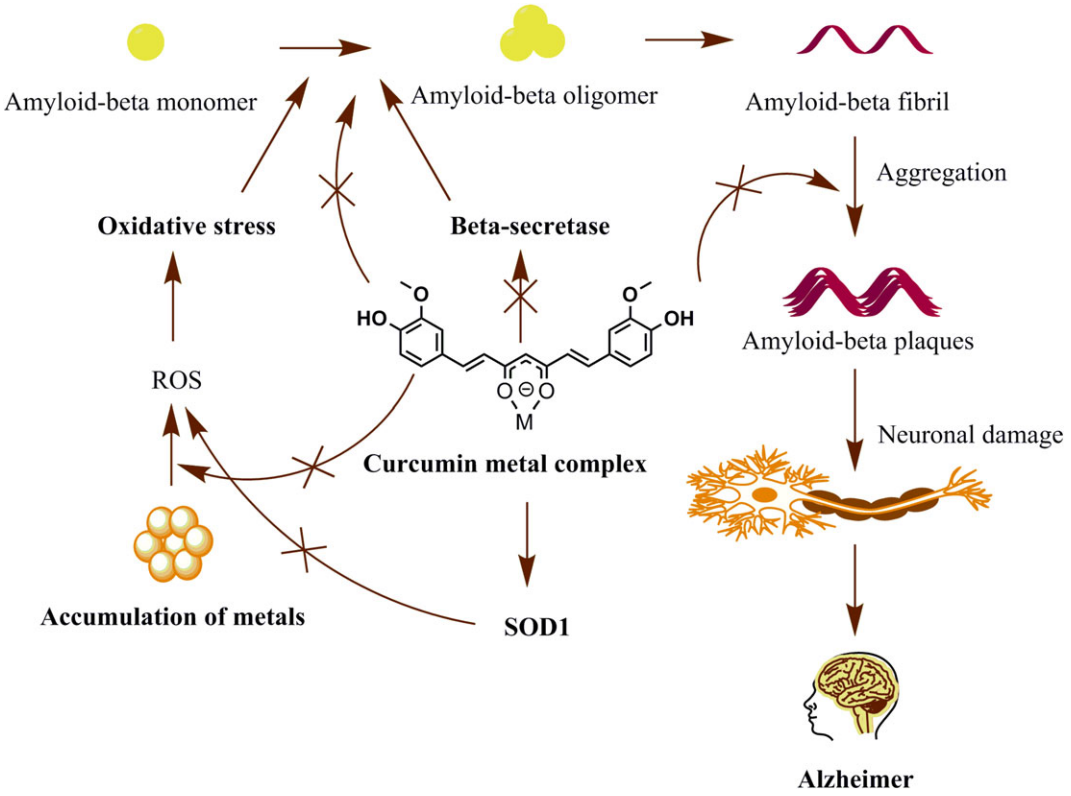

FIG 1 *Schematic representation of the multiple mechanisms of action of metal-complexed curcumin against AD.*

[60]. Oxovanadium (IV) and copper (II) complexes of curcumin enhance its photocytotoxicity approximately five-fold [61]. In addition, several studies have shown that Ru complexes exhibit anticancer activity [35,62]. Furthermore, complexes of Ru^{2+}, because of their nontoxic nature, have high selectivity for tumor cells, likely due to the ability of ruthenium to mimic iron in binding to biomolecules [59,63]. A complex of Ru^{3+} named indazolium trans-[tetrachlorobis (1H-indazole) ruthenate (III)], which is now in phase I clinical trials, has been shown to induce the apoptosis in SW480- and HT29-colorectal carcinoma cells in rats by the intrinsic mitochondrial pathway [64]. Some of the most important metal anticancer compounds are presented in Fig. 2.

Some anticancer metal complexes, including Pt, Au, As, Ru, Rh, Cu, V, Co, Mn, Gd, and Mo, have been demonstrated to either interact with, or even disturb, cellular redox homeostasis, which results in enhanced levels of oxidative stress [67]. However, some of these metal-complexed anticancer drugs, for example, platinum compounds, have several limitations due to their serious side effects, which includes classic toxicity to liver and kidneys normally observed with heavy metals [68]. To solve this limitation, many researchers have focused on non-platinum natural product-based drugs containing a metal. Curcumin and its derivatives have anticancer activity on different types of cancer including melanoma, head and neck, breast, colon, pancreatic, genitourinary, gastrointestinal, lung, prostate, and ovarian cancers [69]. There exist quite diverse mechanisms of action of curcumin as it pertains to anticancer activity. However, several authors' studies have demonstrated that curcumin exerts its anticancer activity by suppressing cancer cell proliferation and metastasis, angiogenesis, and by inducing cell death and apoptosis [70,71]. Angiogenesis plays an important role in cancer development and progression [72,73]; therefore, targeting angiogenesis could be a promising strategy for cancer therapy [71]. It was demonstrated that curcumin-capped copper nanoparticles have inhibitory effects on human breast cancer cell line MDA-MB-231 and angiogenesis [74]. One study reported that curcumin complexation with copper considerably enhanced the antitumor effects of curcumin and its derivatives [75]. In fact, the metal complexation of curcumin with metals involves the β-diketo moiety and results in a more stable and cytotoxic compound to cancer cells [2]. Renfrew et al. [76] have found that the incorporation of curcumin into a Co^{3+} chaperone improved stability, cytotoxicity, and tumor penetration compared to those of the free drug. In another study, metal complexes of curcumin with Cu^{2+}, Zn^{2+}, oxovanadium (VO^{4+}), and Ni^{2+} showed a significant increase in cytotoxicity relative to the free ligand. Among the metal complexes studied, the activity followed the following rank order; $Cu^{2+} > VO^{4+} > Ni^{2+} > Zn^{2+}$ [77]. The protective effects of complexation of curcumin with Cu^{2+} and Zn^{2+} against H_2O_2-induced injury in PC12 cells have also been investigated. Specifically, it was found that a curcumin-Cu^{2+} complex had stronger protective effects than curcumin and a curcumin-Zn^{2+} complex. The previously mentioned complexes also inhibited cell apoptosis

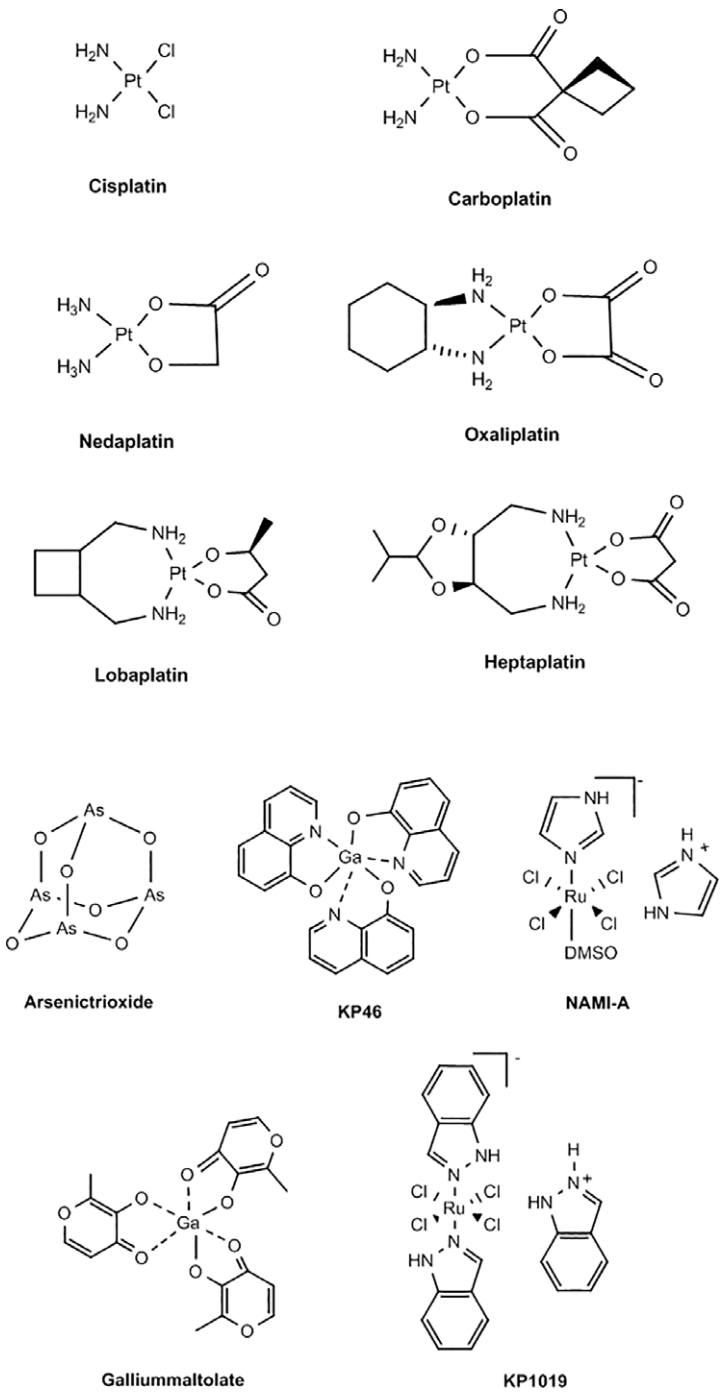

FIG 2 *Some of the most important anticancer drugs complexed with metals [65,66].*

through downregulation of nuclear factor κB (NF-κB) and upregulation of Bcl-2/Bax pathways [78]. A curcumin-manganese complex was also synthetized and evaluated for antiproliferative effects against human osteosarcoma cells (HOS), human colon cancer cells (HT 29), human melanoma cells (A375), and human fibroblast cells (NHDF). Results showed that the manganese complex generated a significant decrease in the IC_{50} for all the tested malignant cell lines when compared to curcumin alone, especially for the HOS and the A375 cell lines [79]. Due to the structural similarity between Pt^{2+} and Pd^{2+} complexes, many authors have investigated the potential anticancer activity of palladium^{2+} complexes and have demonstrated that they are cytotoxic to tumor cells [80,81]. Generally, the complexes of Pd^{2+} showed lower antitumor activity than cisplatin due to their more chemically labile nature [82].

Valentini et al. [83] have evaluated the ability of the Pd^{2+} complexes of curcumin in cell growth inhibition, ROS production, JNK activation, and cell death through mitochondrial bearing membrane depolarization. The complexes induced both cell growth inhibition and apoptosis of human prostate cancer cells (LnCaP, PC3, and DU145) through the production of ROS and JNK phosphorylation associated with GSTp1 downregulation. Additionally, it should be mentioned that curcumin delayed cell growth by inducing G2/M arrest.

Zinc is a cytotoxic/tumor suppressor agent in several cancers. It was found that zinc is decreased in patients in the development of some cancers including breast, liver, prostate, and gallbladder cancers [84]. Suggested mechanisms of action for the anticancer activity of zinc compounds include regulation of angiogenesis [85], the ability to induce apoptosis, and the degradation of the mutant protein-induced autophagy in cancer cells [36]. Furthermore, zinc, as a transition metal with antiulcer activity, induces the expression of heat shock proteins in thermotolerant HeLa cells in vitro [86] and in gastric mucosal and hepatic cells in vivo [87].

Pyrithione zinc, a coordination complex of zinc, is a Food and Drug Administration (FDA)-approved agent that reduces cell proliferation and induces cell death by downregulation in the expression of PI3K/Akt/mTOR and Wnt/β-catenin signaling pathways in oral squamous cell carcinoma [88]. In another study, Fong et al. [89] have found that zinc supplementation rapidly reduced the development of esophageal cancer through the induction of apoptosis in esophageal epithelial cells. Recently, zinc-derived compounds are of increasing interest for their anticancer activity. Interestingly, the anticancer activity of curcumin complexes of Pd^{2+} and Zn^{2+} are similar. Two Zn^{2+} curcumin complexes were prepared and tested for anticancer properties. The results showed promising and selective anticancer properties against DU145, Pc3, and LNCaP cell lines and two neuroblastoma cell lines [90]. The antitumor activity of the two Zn^{2+} complexes against the cell lines mentioned directly above indicated that both derivatives showed strong and selective anticancer properties [35]. Additionally, the antitumor activity of a novel Zn^{2+}-curcumin complex was evaluated against the human colon cancer RKO (wtp53), glioblastoma U373MG (expressing R273H p53 mutation), and T98G (expressing M237I p53 mutation) cell lines. This novel Zn^{2+}-curcumin complex was able to induce DNA damage and conformational changes in p53-R175H and -R273H mutant proteins, which led to the induction of apoptotic cell death [83].

Increased cytotoxic effects of Fe^{3+}-curcumin and Cu^{2+}-curcumin complexes against breast cancer cells MCF-7, MDA-MB-231, and 4T1 has been observed, in which the copper complex of curcumin was more cytotoxic than the iron complex of curcumin [2]. On the

other hand, excess levels of copper have been reported to be related to many diseases like cancer [91]. Insertion of a $–CH^2CH_2COOtBu$ branch in curcumin and complexation with three metals (Ga^{3+}, Fe^{3+}, or Cu^{2+}) showed enhanced stability under simulated physiological conditions and were more cytotoxic (a two-fold enhancement in activity) against human colon carcinoma cells HCT116 compared to curcumin alone [2]. In another study, di-μ-chlorobis [dichlorocurcuminatoniobium(Nb)] dehydrate was synthesized and a statistically-significant decrement in the percent of viable MCF-7 cells exposed to a Nb^{5+}-curcumin complex was observed when compared to normal fibroblast cells exposed to the same Nb^{5+}-curcumin complex [92]. The safety of several compounds containing boron has also been reported [93]. As an example of a drug with boron, bortezomib (Velcade®), a proteasome inhibitor, is now used for the treatment of multiple myeloma (MM) and mantle cell lymphoma in the United States, and clinical trials are underway to assess its efficacy for use in non-Hodgkins lymphoma [94]. However, it has some adverse effects, including peripheral neuropathy and severe constipation [95]. For these reasons, many boron-based natural compounds have been synthesized for medical applications. The cytotoxic activity of curcumin and a curcumin/boron-based complex [curcumin was complexed with 2-aminoethyl diphenyl borate (DPBA)] were tested against the MCF-7 and A549 cancer cell lines. The results demonstrated improved cell penetration/permeation for the curcumin/DPBA complex, without loss of the cytotoxic activity of curcumin [96].

Recently, the anticancer activity of arene Ru^{2+} complexes have been reported. For example, two of them, namely, KP1019 (indazolium trans-[tetrachlorobis(1H-indazole)-ruthenate(III)]) and NAMI-A (imidazolium trans-[tetrachloro(dimethylsulfoxide) (1H-imidazole)ruthenate(III)], are in phase I clinical trials [97]. In addition, the cytotoxic activities of several arene-ruthenium (II) complexes incorporating curcuminoids are being evaluated. Specifically, four neutral compounds bearing amino or hydroxyl groups on the arene ring and curcumin/bisdemethoxycurcumin have been evaluated against human ovarian A2780 and A2780cisR cancer cell lines, as well as nontumorigenic human embryonic kidney HEK 293 cells. The complex with hexamethylbenzene and bisdemethoxycurcumin ligands showed the most cytotoxicity with IC_{50} values of 0.20, 0.27, and 13 μM for A2780, A2780cisR, and HEK293 cells, respectively [98]. It appears that ruthenium complexes are often used to decrease toxicity of active ligands against normal cells by increasing their selectivity to cancer cells. For instance, the cytotoxic effects of a Ru^{2+}-trithiacyclononane curcuminate complex showed that it was nontoxic against normal epithelial prostate cells (PNT-2 line), while curcumin inhibited 65% of the same cells at a concentration of 80 μM [99]. In some cases in which high cytotoxicity has been observed with certain Ru^{2+} complexes of curcumin, the degree of lipophilicity of the ligand has been suggested to play a major role. Caruso et al. have synthesized some arene-Ru^{2+} curcuminoid complexes, and their cytotoxicity was tested on five cancer cell lines including MCF7, A2780, U-87, A549, and HCT116. These authors found that after replacing the hydroxyl groups on curcumin with OCH_3 groups, there was an increased cytotoxic effect of the complexes when compared to curcumin and its related complex [100]. Gallium-68 is used in nuclear medicine imaging techniques for detecting cancerous tissues [101]. Recently, the uptake of three Ga-curcuminoid complexes, namely, Ga $(curcumin)^{2+}$, Ga (diacetylcurcumin, $DAC)^{2+}$, and Ga(bis-dehydroxycurcumin, $bDHC)^{2+}$, was observed by the HT29-colorectal carcinoma cell line, the K562 lymphoma cell line, and a normal fibroblast cell line. Results showed that $Ga(curcumin)^{2+}$ and $Ga(DAC)^{2+}$ exhibited a higher uptake by the HT29 and K562 cell lines than normal lymphocytes, which suggested a possible role of such complexes as potential radiotracers for tumor imaging [102]. On the other hand, while most of the Rh complexes have shown negligible biological properties, nevertheless, the slow release of ligands without any toxicity make them ideal as drug delivery systems for compounds with cytotoxic activity and that possess poor pharmacokinetics properties, for example, curcumin. Markham et al. has reported that the complex [Rh^{3+}(Cp = pentamethylcyclopentadienato)(curcuminato)Cl] effectively delivered curcumin to the A549 lung cancer cell line. In fact, the complex was taken up by cells and enabled the slow intracellular release of curcumin, which subsequently caused cytotoxicity via apoptosis [103].

5. Antimicrobial activity

Curcumin has shown antimicrobial activity in vitro against a wide range of microbes, including several pathogenic gram-positive bacteria such as *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus mutans*, *Staphylococcus epidermidis,* and gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Yersinia enterocolitica,* and *Shigella dysenteriae*, as well as funguses such as *Aspergillus níger*, *Candida albicans,* and *Penicillium notatum* and molds [104]. Gram-positive bacteria show a significantly higher sensitivity to curcumin than the gram-negative bacteria. The outer membrane of gram-negative bacteria is rich in hydrophilic lipopolysaccharides, which acts as a barrier to the effective penetration of a variety of hydrophobic antimicrobial compounds [105]. Curcumin has also been shown to inhibit the biofilm formation of *Enterococcus faecalis* formed on tooth substrates in vitro [106] and has a synergistic effect with various antimicrobial drugs such as gentamicin, cefixime, ciprofloxacin, cefepime, vancomycin, tetracycline, and amikacin against *S. aureus* [107,108]. Despite being extensively studied, little information is available on the exact mechanism(s) of antimicrobial action of curcumin, although it has been reported that the antimicrobial mechanism of action of curcumin includes membrane disruption by inhibiting ATP-ase activity [109,110], as well as the inhibition of bacterial cell proliferation by inhibiting the dynamics of assembly of protein FtsZ in the Z-ring [111], membrane permeabilization [107], production of ROS and antioxidant depletion [112], and biofilm initiation [108]. The nature of metals also plays an essential role in determining the antimicrobial activities of curcumin. In terms of structure–activity relationships, methoxy and hydroxyl groups

TABLE 1 ***Antimicrobial activity of different complexes of curcumin***

Curcumin metal complex	*Microorganisms*	*MIC (μg/ml)*	*Diameter inhibition zone (mm)*	*References*
Cr(Curc)3	*E. Coli*	-	4	Reference 28
	K. pneumonia	-	3	
	Pseudomonas sp.	-	3	
Pd(Curc)2	*E. Coli*	-	2	
	K. pneumonia	-	1	
Y(Curc)3	*E. Coli*	-	1	
	Pseudomonas sp.	-	1.5	
	S. aureus	12.3	-	Reference 117
	B. subtilis	14.1	-	
CuCurCl	*S. typhi*	13.9	--	
	P.aeruginosa	11.8	-	
	E. coli	11.2	-	
CoCurCl	*S. aureus*	12.1	-	
	B. subtilis	14.3	--	
	S. typhi	13.4	-	
	P.aeruginosa	12.1	-	
	E. coli	11.8	-	
NiCurCl	*S. aureus*	12.9	-	
	B. subtilis	14.8	-	
	S. typhi	13.8	-	
	P.aeruginosa	12.6	-	
	E. coli	12.1	-	
ZnCurCl	*S. aureus*	13.0	-	
	B. subtilis	15.0	-	
	S. typhi	14.2	-	
	P.aeruginosa	12.9	-	
	E. coli	12.9	-	
$FeCur(OH)_2$ (in Conc. 200 μg/ml)	*E. coli*	-	1.3	Reference 118
$Cd\ (Cur)_2$ (in Conc. 500 ppm)	*Penicillium verruculosum*	-	18	Reference 119
	Aspergillus niger	-	13	

TABLE 1 *(Continued)*

Curcumin metal complex	*Microorganisms*	*MIC (μg/ml)*	*Diameter inhibition zone (mm)*	*References*
	Aspergillus heteromorphus	-	18	
	Aspergillus flavus	-	20	
	B. cereus	-	19	
Pb $(Cur)_2$ (in Conc. 500 ppm)	*P. verruculosum*	-	15	
	A. niger	-	13	
	A. heteromorphus	-	15	
	A. flavus	-	19	
	B. cereus	-	14	
Hg $(Cur)_2$ (in Conc. 500 ppm)	*P. verruculosum*	-	17	
	A. niger	-	19	
	A. heteromorphus	-	17	
	A. flavus	-	24	
	B. cereus	-	17	
Sn $(Cur)_2$ (in Conc. 500 ppm)	*P. verruculosum*	-	22	
	A. niger	-	20	
	A. heteromorphus	-	19	
	A. flavus	-	15	
	B. cereus	-	20	
Ca $(Cur)_2$ (in Conc. 500 ppm)	*P. verruculosum*	-	17	
	A. niger	-	15	
	A. heteromorphus	-	15	
	A. flavus	-	14	
	B. cereus	-	16	
Cu $(Cur)_2$	*S. aureus*	-	40	Reference 120
	E. coli	-	43	
	Klebsiella pneumonia	-	47	
	Pseudomonas fluorescence	-	32	
di-l-chlorobis [dichlorocurcuminatoniobium (V)] dehydrate (in Conc. 1 μg/μl)	*E. coli*	-	20	Reference 92
	P. aeruginosa	-	30	
	M. luteus	-	17	
	S. aureus	-	18	

TABLE 1 *(Continued)*

Curcumin metal complex	*Microorganisms*	*MIC (μg/ml)*	*Diameter inhibition zone (mm)*	*References*
[CuCurCl]Cl (in Conc. 0.001 M)	*Penicillium digitatum*	-	12	Reference 121
	Streptococcus pyogenes	-	23	
	S. aureus	-	10	
	A. flavus	-	17	
[CoCurCl]Cl (in Conc. 0.001 M)	*P. digitatum*	-	16	
	S. pyogenes	-	14	
	S. aureus	-	10	
	A. flavus	-	13	
[NiCurCl]Cl (in Conc. 0.001 M)	*P. digitatum*	-	15	
	S. pyogenes	-	13	
	S. aureus	-	12	
	A. flavus	-	13	
[ZnCurCl]Cl (in Conc. 0.001 M)	*P. digitatum*	-	15	
	S. pyogenes	-	12	
	S. aureus	-	11	
	A. flavus	-	14	

are suggested to play a crucial role in the antimicrobial activity of curcumin [113]. In addition, hydrogen bonding and charge delocalization are the two main physicochemical properties of curcumin for facilitating the interactions with the outer bacterial cell wall [114]. The replacement of these phenolic protons by suitable metals may enhance the antimicrobial activity of curcumin. For thousands of years, metals such as mercury, arsenic, copper, and silver have been used for their antimicrobial properties [115]. Most of the metals with antimicrobial activity are typically the metals of the d-block (V, Ti, Cr, Co, Ni, Cu, Zn, Tb, W, Ag, Cd, Au, and Hg), and a few other metals are from groups 13–16 of the periodic table (Al, Ga, Ge, As, Se, Sn, Sb, Te, Pb, and Bi) [116]. Antimicrobial activity of complexes of curcumin with several metals is shown in Table 1. The formation of a curcumin-complex with several metals is well documented in the literature and serves as an alternative to overcome the limitations associated with effective antimicrobial activity of curcumin alone. For example, Hatamie et al. have shown enhanced antimicrobial activity of cobalt-curcumin as compared to either cobalt alone, or curcumin alone [122]. The antimicrobial activity of metal complexes of curcumin with Cr^{3+}, Pd^{2+}, Y^{3+}, La^{3+}, Ce^{3+}, and Eu^{3+} have been evaluated, and it has been shown that among these metals, Cr^{3+}, Pd^{2+}, and Y^{3+} exhibited antibacterial activity against *E. Coli*, *Klebsiella pneumonia*, and *Pseudomonas* sp [28]. Additionally, curcumin diketimine complexes with Cu^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} were synthesized and their antibacterial activities against *Streptococcus pyogenes* and *S. aureus* and antifungal activities against *Aspergillus flavus* and *Penicillium digitatum* were tested. The results demonstrated that most of these complexes had greater antibacterial and antimycotic activity than curcumin alone. Among them, the Cu(II) complex was more active than amikacin (used as a positive control) against *S. aureus* [121]. The antifungal (*Aspergillus niger, Aspergillus flavus, Aspergillus heteromorphus*, and *Penicillium verruculosum*) and antibacterial (*B. cereus*) activities of metal complexes of curcumin with Cd^{2+}, Hg^{2+}, Pb^{2+}, Sn^{2+}, and Ca^{2+} have also been evaluated. The results showed that metal complexation enhanced the activity of curcumin, and among the metal-curcumin complexes, the Sn^{2+} complex showed the best activity except for *A. flavus,* whereas, the Hg^{2+} complex was more active toward *A. flavus* [119]. Also, several complexes of Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} with curcumin were synthesized, and their antimicrobial activity was investigated against *E. Coli*, *S. aureus*, *B. subtilis*, *P. aeruginosa*, *A. flavus*, and *C. albicans.* However, when curcumin was complexed with the metals mentioned directly above, they did not show significant microbial inhibition, except for the Co^{2+}-curcumin complex, which exhibited a mild antibacterial

activity toward *B. subtilis*, *P. aeruginosa*, and *S. aureus* [123]. The antibacterial activity of In^{3+}-curcumin, In^{3+}-diacetylcurcumin, and diacetylcurcumin, along with curcumin, were tested against *S. aureus*, *S. epidermidis*, *P. aeruginosa*, and *E. coli.* In^{3+}-curcumin showed antibacterial activity against all bacteria, whereas In^{3+}-diacetylcurcumin was effective against *S. epidermidis* and *P. aeruginosa.* Diacetylcurcumin showed no antimicrobial activity with the bacteria tested. The antibacterial activity of In^{3+}-curcumin (MIC = 93.8 μg/ml for *S. aureus* and 23.4 μg/ml for *S. epidermidis*) was greater than curcumin itself (with MIC of 187.5 μg/ml for *S. aureus*, and 46.9 μg/ml for *S. epidermidis*) [124]. Liao et al. have used tannic acid and transition metals (Fe^{3+} and Cu^{2+}) to coat curcumin nanoparticles for investigation of their antibacterial effects. The Cu^{2+} complex had similar antibacterial activity with Fe^{3+} against *E. coli*, although it showed better activity against *S. aureus* than the Fe^{3+} complex. The MIC of the nanoparticles utilizing the Cu^{2+}-curcumin complex was improved 200-fold and 7.5-fold compared to Cu^{2+} alone and curcumin alone, respectively [125]. Several curcumin-based metallointercalators with the oxygen and nitrogen of cysteine coordinated to either the transition metals Cu^{2+}, Co^{2+}, Ni^{2+}, or Zn^{2+} were synthesized and evaluated for their antibacterial activity against *S. aureus, B. subtilis, E. coli, P. aeruginosa, S. typhi*, and antifungal activity against *A. niger, F. solani, C. lunata, R. bataicola,* and *C. albicans.* All the metal complexes exhibited considerable antimicrobial activity compared to the ligand (curcumin) alone with the rank order of $Cu^{2+} > Co^{2+} > Ni^{2+} > Zn^{2+}$ [117]. A summary of the antimicrobial activity of different metal complexes of curcumin is presented in Table 1.

6. Antiviral activity

There are a number of antiviral drugs approved for clinical use. However, the treatment of infectious diseases presents several challenges, because of insufficient drug efficacy, drug toxicity, and the high cost of current antivirals. Thus, exploring novel strategies and/or the use of safe and effective natural products represents an urgent need to combat viruses [126]. Curcumin has shown antiviral activity against numerous viruses including dengue virus (serotype 2), human immunodeficiency virus, Japanese encephalitis virus, pseudorabies virus, vaccinia virus, parainfluenza virus type 3 (PIV-3), feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), herpes simplex virus (HSV), flock house virus (FHV), respiratory syncytial virus (RSV), hepatitis viruses, influenza type A virus (IAV), Ebola virus, and arthropod-borne viruses [126–128]. Different possible mechanisms have been reported for curcumin's antiviral properties such as functioning as an HIV-1 integrase inhibitor [129], degrading viral Tat protein [130], inhibiting proteases [131], inhibiting viral entry [132], inhibiting virus attachment to cells [133], and inhibiting viral replication [134]. Antiviral properties of several metal complexes have been reported [135,136]. For example, a copper-curcumin complex was synthesized by Chauhan et al. and its antiviral activity against numerous viruses, including the herpes simplex virus strains, vaccine virus, vesicular stomatitis virus, coxsackie virus b4, respiratory syncytial virus, para-influenza-3 virus, reovirus-1, sindbis virus, and punta toro virus was investigated. Their results showed that the copper-curcumin complex had good antiviral properties against vesicular stomatitis virus, coxsackie virus B4, and respiratory syncytial virus [137]. In another study, boron complexes of curcumin were prepared and their anti-HIV potential was tested. It was shown that some complexes had potent inhibitory activity toward HIV-l and HIV-2 proteases. The elevated affinity of boron complexes of curcumin is likely associated with the attachment of the orthogonal domains of the compound in intersecting sites within the substrate-binding cavity of the protease [131]. In addition, Ga^{3+} and Cu^{2+} complexes of curcumin showed substantial antiviral effects against HSV-1 (IC_{50} values of 13.9 and 23.1 μ/mL, respectively) compared to curcumin alone, which had an IC_{50} value of 33.0 μ/mL [138].

7. Atherosclerosis

It is well known that inflammation has a critical role in all stages of atherosclerosis pathophysiology [139–142]. In fact, atherosclerosis is an inflammatory response of arterial wall to injuries promoted by risk factors such as dyslipidemia, diabetes, hypertension, and others [143]. Therefore, anti-inflammatory agents could be a good candidate for treatment of the mentioned conditions. Curcumin can inhibit atherosclerosis through tuning cholesterol transport homeostasis and modulating inflammatory response in M1 macrophages [144]. Curcumin also showed antiatherosclerosis through upregulation of thrombospondin-4 (THBS-4) in mouse macrophages treated with oxidized low-density lipoprotein [145]. There is also compelling evidence showing the modulating effects of curcumin on macrophage chemoattractant protein-1 (MCP-1) [146], which is involved in the pathogenesis of several inflammatory diseases including atherosclerosis [147]. In addition, it was demonstrated that curcumin could be effective in patients with diabetes-related atherosclerosis [148]. To the best of our knowledge, little data are available on the effect of metal-complexes of curcumin on atherosclerosis-related diseases. A significant reduction in blood glucose, glycosylated hemoglobin (Hb)A1c, and lipid profile parameters were observed by oral administration of cur-Zn complex in diabetic rats compared to curcumin alone [149]. In another study, curcumin models lacking aromatic peripheral hydroxyl and methoxy groups, along with some metal derivatives showed inhibitory effect on the intercellular adhesion molecule-1 (ICAM-1), in which 4-benzoyl-3-methyl-1-phenyl-pyrazol-5-one among the ligands, and sodium benzoylacetonato among metal derivatives were the best inhibitors [150].

8. Conclusions

This review provided an overview of the therapeutic applications of different metal complexes of curcumin. Over the last several decades, the use of several organometallic compounds

containing copper, ruthenium, zinc, arsenic, silver, gold, cobalt, titanium, aluminum, and iron has attracted interest for the development of new therapeutic agents. Metal-based compounds have many advantages. One advantage of using metal-based compounds is that both the metal and the organic ligands each possess or exert individual physicochemical/biological properties. For example, the presence of strong covalent bonds increases the stability of the compound in a biological environment and may, therefore, influence the biological activity of the organic compound complexed with the metal atom. In addition, metal complexes, as an important class of therapeutic agents in the field of medicine, show the potential to overcome the limitations of many drugs with regard to drug selectivity, resistance, and toxicity. Although the clinical applications of some of these compounds are discussed throughout this review, their clinical use is sometimes associated with several side effects. However, since some data suggest that metallocomplexes of curcumin are often less toxic than curcumin itself, there has been considerable attention toward the design of metal complexes of curcumin to overcome the drawbacks associated with curcumin's clinical application (e.g., low aqueous solubility, low overall bioavailability, rapid clearance, etc.). As discussed above, in most cases, the binding of a metal to curcumin improves its biological activity, its physicochemical stability in a biological milieu, and its aqueous solubility. However, the biological properties of metallocomplexes of curcumin and its derivatives depend on several factors, including the central metal utilized, the ligand, and its associated structural chemical modifications, the overall molecular shape and dimensions of the resulting complex, exchange capability of the ligand, and the net ionic charge of the complex [151]. Meanwhile, there is virtually no data on the pharmacokinetic properties of most of these metalcurcumin complexes following introduction into the human body. Therefore, more in vitro and in vivo studies, as well as clinical trials, are needed for the successful development and ultimate medical applications of these novel metallocomplexes of curcumin.

Conflict of Interests

None.

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