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Review Article

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Metal–Curcumin Complexes in Modern Pharmacotherapeutics: A Comprehensive Review

Maheshwar Rathore[1], **Arin Bhattacharya**[2*]

[1]Department of Pharmaceutical Chemistry, J. K. College of Pharmacy, Bilaspur 495001, Chhattisgarh, India; [2]Department of Pharmacology, J. K. College of Pharmacy, Bilaspur 495001, Chhattisgarh, India.

ABSTRACT

The major ingredient in turmeric, curcumin, has drawn a lot of interest as a plant-based substance having pharmacological benefits that are pleiotropic. It has immunomodulatory, neuroprotective, antibacterial, anti-inflammatory, antioxidant, hypoglycemic, and anti-inflammatory properties. Curcumin has certain health-promoting properties, but they are limited by its hydrophobicity, insolubility in water, low bioavailability, quick metabolism, and systemic elimination. Complexes of metals with curcumin have been created as a result of this unique step. The -diketone moiety of curcumin often interacts with metals to form metal-curcumin complexes. It is generally known that the metal ions of boron, cobalt, copper, gallium, gadolinium, gold, lanthanum, manganese, nickel, iron, palladium, platinum, ruthenium, silver, vanadium, and zinc are all highly chelated by curcumin. Metal-curcumin complexes' pharmacological, chemo-preventive, and therapeutic properties are described in this paper. Metal-curcumin complexes boost the antioxidant, anti-inflammatory, antibacterial, and antiviral properties of curcumin by increasing its solubility, cellular absorption, and bioavailability. Additionally, metal-curcumin complexes have shown effectiveness against a number of chronic illnesses, such as cancer, rheumatoid arthritis, osteoporosis, and neurological conditions including Alzheimer's disease. The regulation of inflammatory mediators, transcription factors, protein kinases, antiapoptotic proteins, lipid peroxidation, and antioxidant enzymes was linked to these biological activities of metal-curcumin complexes. Metal-curcumin complexes have also proven beneficial in radio-imaging and biological imaging. Future applications of metal-curcumin complexes might signal a fresh strategy for the management of chronic illnesses.

Keywords: Curcumin, Metal, Complex, Synthesis, Therapeutics, Diagnostics

INTRODUCTION

Turmeric contains a hydrophobic yellow crystalline polyphenol called curcumin (**Figure 1**), also known as diferuloylmethane (*Curcuma longa*). It is one of the main members of the curcuminoid family, along with desmethoxycurcumin and bis-desmethoxycurcumin, two additional curcuminoids. Since it gives food a unique color and flavor, turmeric has been utilised as a spice in many Southeast Asian nations. However, curcumin is also utilised as a traditional medicine to treat a wide range of chronic illnesses, such as metabolic, autoimmune, respiratory, pulmonary, neurological, and cardiovascular disorders. Additionally, it has been shown to be useful in treating sinusitis, cough, coryza, hepatic disorders, and anorexia.[1,2] Curcumin's pleiotropic pharmacological features have been linked to both its therapeutic and preventative benefits. Curcumin may have anti-inflammatory, antioxidant, wound-healing, hypoglycemic, and antibacterial effects, according to growing data.[3]Curcumin has remarkable biological effects, yet it still has certain physical limitations, such as low bioavailability and insolubility in water.

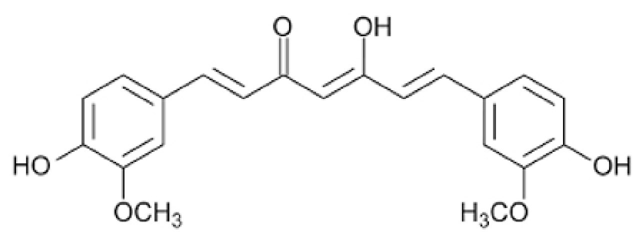

Figure 1: Structure of curcumin.

To get around these issues, changes to its structure have been made during the past few decades, including the creation of curcumin analogues. Feruloyl groups replace two hydrogens in the structure of curcumin, a beta-diketone. Keto and enol are two of the at least two tautomeric forms that are known to exist. While the enol form of curcumin

Corresponding Author:
Dr. Arin Bhattacharya, Professor, Department of Pharmacology, J. K. College of Pharmacy, Bilaspur 495001, Chhattisgarh, India.
Phone: +91-7869529756; E-mail: arinpharma@rediffmail.com

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only occurs in alkaline pH environment, the keto form does exist in acidic and neutral pH media.[4] Curcumin has three significant functional groups and a seven-carbon linker as part of its structure. An aromatic O-methoxy-phenolic group, α, β-unsaturated-diketone moiety, and a seven-carbon linker molecule make up these functional groups. The aromatic rings of curcumin are connected by two, α, β-unsaturated carbonyl groups. In contrast to the, α, β-unsaturated carbonyl, which serves as a Michael acceptor and undergoes nucleophilic addition, diketones readily deprotonate themselves to create enolates.[5] The phenolic group in curcumin is what gives it its antioxidant properties, but the carbon linker molecule gives it its hydrophobicity. [6] Curcumin has been physically altered to boost its biological action since it is naturally hydrophobic.

Complexes of curcumin with different metals have been created recently to address curcumin's drawbacks and increase its biological potency (**Figure 2**). The interaction between metals and the curcumin ligand modifies the overall structure of the compound, increasing its biological potency. It has been demonstrated that the metal ion coordination causes the carbonyl group at the diketone moiety to become instabilized.[7] Due to the fact that metals are recognised as an enzyme coactivator, complexes of curcumin and metal can interact with the active sites of enzymes and trigger a variety of cellular activities. Although complexes of curcumin in the form of nanoparticles, liposomes, micelles, and phospholipids have been created and have demonstrated improved biological efficacy, [8] complexes of curcumin with transition metals may offer an alternative strategy to deal with the problems curcumin is known to have.

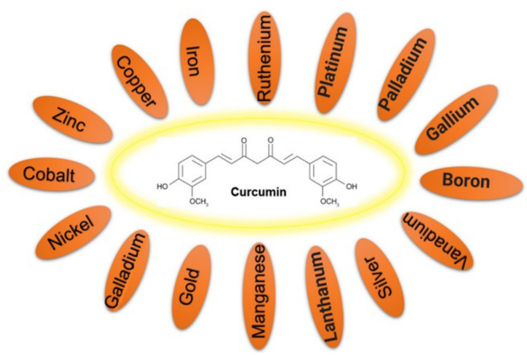

Figure 2: Metal–Curcumin Interactions.

Metal–Curcumin Interactions

Curcumin interacts with numerous metal ions due to the fact that its,-unsaturated β-diketo moiety is said to be a potent chelating agent. The binding of metals to curcumin has been studied using a variety of methods, including atomic force microscopy (AFM), UV-Vis spectroscopy, Fourier transform infrared, nuclear magnetic resonance, and mass spectroscopy. Curcumin's keto-enol (-di-ketone moiety) group often binds to metals via chelation. Chelation is a specific kind of chemical bonding that takes place when a metal cation and at least one multidentate ligand create dative covalent bonds, sometimes referred to as coordinate bonds. Dative covalent bonds contain electrons furnished by only one atom, as opposed to traditional covalent connections, which share electrons from both atoms. This bond has a semipolar structure. The curcumin undergoes a structural change as a result of this chelation bond interaction. [9] Normally, metals only bind one or two molecules of curcumin, nevertheless, binding of three molecules of curcumin has also been shown, for example, an octahedral complex with Fe^{3+} .[10] As the enolic proton is replaced by a metal ion and the o-methoxy phenolic group is left intact in the complexes, metals can be coordinated with curcumin by its enolic group. All four of the metal-O bond lengths in the complex differ when one metal binds to curcumin in a 1:1 ratio, but they all differ when one metal binds to curcumin in a 1:2 ratio. In contrast to the 1:2 metal-curcumin complex, which has been shown to have square planar coordination around the metal, metal-curcumin (1:1) also induces orthorhombic symmetry in the structure. Additionally, it has been noted that the methoxy groups of the phenolic rings in both of the curcumins in the 1:2 metal-curcumin complex exhibit steric repulsion. [11]

The periodic table has around 80 elements that are classified as metals. Others metals are used as the foundation for everyday engineering, some for medicinal applications, and some for both. Their particular chemical and physical features, such as ionic state, physical geometry, valence bonding, and other chemical traits, determine how they are employed. When making curcumin-metal complexes, these chemical properties, which vary from one metal to another, can be utilised for a number of medicinal applications. Curcumin's physical, chemical, and biological characteristics are all impacted by the development of complexes containing metals, as well as the metals' biological reactivity. Curcumin-metal compounds typically lessen the toxicity of metals. [5] New metal-based antioxidants can be produced by complexation with particular metals, such as Cu^{2+} and Mn^{2+}.

Synthesis of the Curcumin–Metal Complexes

With practically all metal ions and nonmetals, curcumin functions as a ligand and creates stable complexes. Metal-curcumin complexes have been created so far using a variety of techniques. It is important to get both the metal and the curcumin in solution form for the reaction to take place and result in the formation of a curcumin-metal complex. Curcumin must be dissolved in a variety of organic solvents because it is very little soluble in water. Methanol, ethanol, and acetone are examples of common solvents that can be used. The metals employed in the process, on the other hand, are often in the form of salts, which may be dissolved in water. In addition to being soluble in water, some metal salts, like $ZnCl_2$, are also soluble in some organic solvents, such methanol. Depending on the metal, it may be feasible to carry out the chelation process using solvents without harming the environment, as opposed to using organic solvents. By mechanically combining metal chloride salts and curcumin (metal ion:curcumin 1:1 mol with Zn^{2+}, 1:3 with Fe^{3+}) in a mortar until uniform powder mixes were produced, Hieu et al. [14] for instance created metal-curcumin complexes. To create powdered complexes of the curcumin metal ion, a propylene glycol:water (1:1 v/v) solution was added to the mixtures, which were then mechanically shaken and dried at 60°C. The synthesis of a curcumin complex with lanthanum metal using a more conventional organic solvent method involves adding a curcumin solution in ethanol to a La $(NO_3)_3$• $6H_2O$ solution (also in ethanol) at pH 6, followed by refluxing at 80°C. Similar to this, a Pd-curcumin complex was created by combining a solution of $PdCl_2$ with a solution of curcumin and Na_2CO_3 in methanol, then heating the combination at 60°C until a clear, blood-red solution was obtained. [15]

Pharmacological Effects of Metal–Curcumin Complex

Compared to free curcumin, curcumin-metal complexes have better pharmacological effects. These compounds can increase antioxidant activity, reduce inflammation, fight against infections and cancer, as well as display gastroprotective and neuroprotective properties.

Antioxidant

Complexes of metal and curcumin have a variety of recognised uses. They have been described as having "multi-anti" properties as a result, [37] such as having different pharmacological activities including antioxidant actions that are superior than either free curcumin or free metal ions alone. Tetrahydrocurcumin, a metabolite of curcumin, and other curcuminoids have antioxidant properties that are helpful for treating a variety of medical ailments. [4] Curcumin is one of the most significant antioxidant herbs, particularly from a commercial aspect, among the many other plants that have these qualities. The antioxidant curcumin is hypothesised to disrupt phenolic chains by donating H^+ atoms from the phenolic group. [38] Curcumin also inhibits the production of free radicals by increasing the quantities and activity of antioxidant enzymes such glutathione peroxidase, superoxide dismutase, and catalase. [39] To demonstrate its effectiveness, various preclinical and clinical experiments have been conducted. In fact, malondialdehyde (MDA) concentrations have been observed to tend to decrease when curcumin supplementation is given to people. [40]

Metal-curcumin complexes regulate oxidative stress by either lowering free radicals, increasing antioxidant levels, or doing both, as oxidative stress is brought on by an imbalance between the body's free radicals and antioxidant state. According to the majority of studies, curcumin-metal complexes are more effective in fighting free radicals than curcumin alone. [7,14,41,42] At the same dose, curcumin complexes containing Cu^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}, and Fe^{2+} shown superior ferrous-reducing and DPPH radical scavenging abilities to free curcumin. According to one research, the metal:curcumin ratio (1:1) is more effective than the metal:curcumin ratio (1:2) in scavenging superoxide anion radicals (via proton transfer or electron transfer) but less effective at scavenging DPPH radicals (through H-atom transfer). [11] When complexed with curcumin, zinc seems to have an improved capacity to boost antioxidant activity. This could be as a result of zinc's superiority over manganese or iron in stabilising the interaction energy of metal complexes with free radicals. [7] It has been discovered that administering a Zn^{2+}-curcumin complex reverses the lowered antioxidant enzyme activities and raises the MDA level brought on by cold-restraint stress in an animal model. [17] Another combination of Fe^{2+}-curcumin enhanced the antioxidant activity of curcumin while also retaining antioxidant enzyme activity during chelation. [18] Thus, by lowering oxidation, this compound may function as a medicinal agent.

The DPPH radical test has revealed that curcumin-capped gold nanoparticles and curcumin-silver nanoparticles both exhibit high antioxidant activity. [19,20] When compared to free curcumin, it has been demonstrated that the curcumin-Cu^{2+} combination has higher superoxide scavenging abilities. The activity of antioxidant enzymes including catalase, superoxide dismutase, and glutathione peroxidase are also improved by curcumin-Cu^{2+} or -Zn^{2+} complexes, and the rise in MDA levels in rat neural pheochromocytoma (PC12) cells is reduced. [21] Additionally, it has been shown that the Cu^{2+}-curcumin combination exhibits potent anti-DPPH radical action. [11] Utilizing the DPPH free radical scavenging assay and the ABTS+ assay, the antioxidant activity of another curcumin complex produced with chitin-glucan-based zinc oxide nanoparticles were calculated. Curcumin was discovered to boost the complex's antioxidant activity when it was loaded into zinc oxide nanoparticles. [22] Additionally, it was demonstrated that complexes of ruthenium metal with curcumin have stronger antioxidant activity than dosages of curcumin alone utilising the DPPH and ABTS+ tests [23]. Mice exposed to cadmium were used to test the Mn2+-curcumin complex's antioxidant effects. Unchelated curcumin and Mn-curcumin complexes have been found to restore hepatic glutathione (GSH) levels and inhibit the growth of hepatic lipid peroxidation, albeit no potentiation was seen. [43] Studies on the diacetylcurcumin-gallium complex, a derivative of curcumin, have demonstrated that it exhibits antioxidant activity that is more effective than curcumin. [24] The antioxidant properties of diacetylcurcumin-metal complexes were further supported by research. The reduction in lipid peroxidation is evidence of the beneficial antioxidant effects of the diacetylcurcumin-metal (Mg, Zn, Cu, and Mn) complexes. [44]

It appears that metal stabilises curcumin in the complex when a superoxide radical attaches to it, which may be one reason why curcumin-metal complexes seem to be more effective antioxidants. [11] When a superoxide radical combines with a metal, such as copper, that has formed a complex with curcumin, the complex may withstand the deformation from a square-planar geometry to a deformed tetrahedral geometry. When free radicals attach to curcumin, the substance has the ability to readily oxidise and subsequently change structurally. A curcumin-metal complex can continue to exist because the binding of metal ions to curcumin does not significantly alter the physical shape of the compound. When free radicals attach to the phenolic structure of the curcumin, the metal stabilises the curcumin structure. When a free radical comes into contact with the phenolic portion of curcumin, the electron is spread across the phenolic ring structure while also changing the curcumin molecule's overall structure. The overall structure of the compound appears to be stabilised by the metal, making it easier for the curcumin-metal complex to receive the additional free radical electron than just curcumin by itself. This causes curcumin to undergo several redox cycles and display greater antioxidant activity. A curcuminoid's phenolic structure appears to be the location of free radical interaction, with the keto-enol moiety playing a minor role. [41] This is in line with the theory that antioxidants' aromatic ring topologies can delocalize unpaired electrons and so aid in the elimination of free radical characteristics.

Antimicrobial

The antibacterial properties of curcumin against a variety of bacterial species are well established. It has been demonstrated that curcumin is more sensitive to Gram-positive bacteria than to Gram-negative bacteria. [47] Curiously, exposure to light might increase the antibacterial action of curcumin even more. However, a compound including metal or curcumin nanoparticles was produced, which significantly boosted curcumin's antibacterial activity. [48,49] In bacterial growth curves of *Escherichia coli* and *Bacillus subtilis*, it has been discovered that metal-curcumin-conjugated DNA complexes exhibit a prolonged lag phase, [9] confirming their bacterial growth-suppressing activities. The antibacterial efficacy of curcumin complexes with Co^{2+}, Ni^{2+}, and Cu^{2+} ions against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes* was also evaluated. The strongest antibacterial activity was found in the Cu^{2+}-curcumin combination. The relative order of antibacterial activity, however, was $Cu^{2+} > Ni^{2+} > Co^{2+} >$ (L) for *S. pyogenes*, *S. aureus*, and *E. coli*, but for *P. aeruginosa* and *K. pneumoniae*, it was $Cu^{2+} > Co^{2+} > Ni^{2+} >$ (L). Additionally, these compounds have anthelmintic effects in *Pheretimaposthuma*. It's interesting to note that the Co^{2+} and Ni^{2+} follow the Cu^{2+}-curcumin complex to maximise effectiveness. [29]

It has been demonstrated that a Zn2+-curcumin combination has extreme toxicity toward *P. aeruginosa.* [30] Similar results were obtained with a curcumin combination that contained chitin glucan-zinc nanomaterial. [22] Antimicrobial activity of the Ru^{2+}-curcumin complex has been found, notably against the drug-resistant Gram-positive *S. aureus*. In addition to having good selectivity, this compound exhibited inhibitory action against a number of methicillin- and vancomycin-resistant *S. aureus* strains. In addition, compared to vancomycin, this compound reduced mean bacterial counts in a mouse model of *Staphylococcus* infection. These findings suggest that both *in vitro* and *in vivo* models of the Ru^{2+}-curcumin complex have strong antibacterial potential. [31]

When compared to free curcumin, the Mn^{2+}-curcumin complex has been found to significantly increase antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. [32] In comparison to curcumin alone, another rare earth metal and curcumin combination (rare earth(III) nitrate) also displayed considerable antibacterial action. [50] Along with having high water solubility, a compound of silver nanoparticles and curcumin has also demonstrated improved antibacterial activity. As a result, this compound demonstrated the potential to stop bacterial infections of wound surfaces. [20] It has been proposed to create a vaginal microbicidal gel using the Cu^{2+}-curcumin complex since it also has a positive microbicidal action. [33] Another research found that the minimum inhibitory concentrations (MIC) of Cu^{2+}-curcumin complexes and free curcumin were 62.5 µg/mL and 125 µg/mL, respectively, and that the former displayed greater growth inhibition of *P. aeruginosa* than the latter. Cu^{2+}-curcumin complexes (62.5 µg/mL) also slowed the development of bacterial. [34]

Metal-curcumin complexes also prevent the development of bacterial biofilms in addition to their microbial inhibitory actions. An orthovanadium-curcumin complex's ability to suppress the development of bacterial biofilms was examined in one research. *In silico* investigations revealed a favorable correlation between the suppression of bacterial alkaline phosphatase activity and the reduction of this complex's ability to inhibit Gram (+) bacteria *S. aureus* and Gram (-) bacteria *E. coli* culture-associated biofilms.[35] Another study found that *P. aeruginosa* was highly inhibited from forming biofilms, swarming and twitching motilities, and producing alginate and pyocyanin when a Cu^{2+}-curcumin complex was applied at a concentration of 1/4 MIC.[34] This finding supports the effectiveness of the compound in the treatment and management of *P. aeruginosa* infections. When compared to several FDA-approved medications, the curcumin-ruthenium compound displayed substantial antibiofilm action.[31] The Zn^{2+}-curcumin combination has further demonstrated effectiveness against biofilm development in addition to these.[30] According to these researches, curcumin-metal complexes show antimicrobial action via increasing toxicity, reducing growth, and preventing the development of biofilms.[51]

CONCLUSION

In comparison to conventional methods using curcumin alone, the capacity of certain metals to complex with curcumin is unquestionably a better method for treatment modalities for a variety of health issues present in both people and animals. It has been demonstrated that curcumin-metal complexes have more antioxidant, anti-inflammatory, antibacterial, and antiviral effects than curcumin alone. These curcumin-metal complexes can be utilised to treat a variety of illnesses and health issues that affect both people and animals, including cancer, osteoporosis, neurological disorders, and arthritis. For some medical situations, some metals are superior to others. Future studies will focus on identifying which metals paired with curcumin have more advantageous benefits for particular disorders. The use of copper- and zinc-curcumin complexes for antioxidant and anti-inflammatory properties, copper-curcumin complexes for antimicrobial activity, boron-curcumin complexes for antiviral activity, copper-, zinc-, and ruthenium-curcumin complexes for cancer, lanthanide-curcumin complexes for osteoporosis, or the use of boron-curcumin complexes for diabetes have all been covered in this It is yet unknown which metal complex will be the most useful for a given medical application. However, many health issues linked to oxidation and inflammation may benefit from zinc-curcumin complexes in particular. Many inflammatory disorders have an underlying cause that involves oxidation. With regard to oxidation and inflammation, it is well known that both zinc and curcumin have positive effects on the immune system. Zinc is essential for immune system maintenance because it supports the activity of immune system enzymes. For instance, it is well known that rheumatoid arthritis (RA) patients have much lower zinc concentration than healthy persons. More severe illness is correlated with the lowest values. Zinc supports the immune system and cartilage, which may help to reduce the symptoms of RA. By regulating cartilage deterioration, zinc may potentially be used as a supplement to normalise osteoarthritis in people. As a result, the usage of zinc-curcumin complexes may be beneficial for inflammatory disorders since they enable the delivery of the necessary zinc as well as the advantages of curcumin. Additionally, as zinc has antiviral properties, using zinc-curcumin complexes may possibly be particularly beneficial for viral infections. The future of these curcumin-metal complexes clearly offers enormous potential for better treatment and prevention in a wide variety of health issues, even if the many individual metals employed in these complexes are still being studied for maximum performance.

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Conflict of Interest

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Authors' Contribution

AB: Concept, Guidance, Revisions

MR: Writing, Corrections

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