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Metal–Curcumin Complexes In Modern Pharmacotherapeutics: A Comprehensive Review

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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 β-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, chemopreventive, 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 radioimaging and biological imaging. Future applications of metal-curcumin complexes might signal a fresh strategy for the management of chronic illnesses.

Index Terms - Curcumin, Metal, Complex, Synthesis, Therapeutics, Diagnostics.

1. 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.

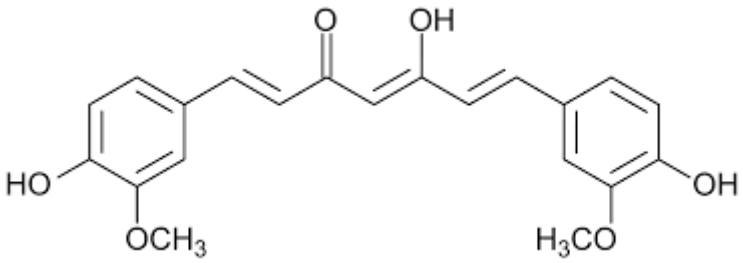

Figure 1. Structure of curcumin.

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 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.

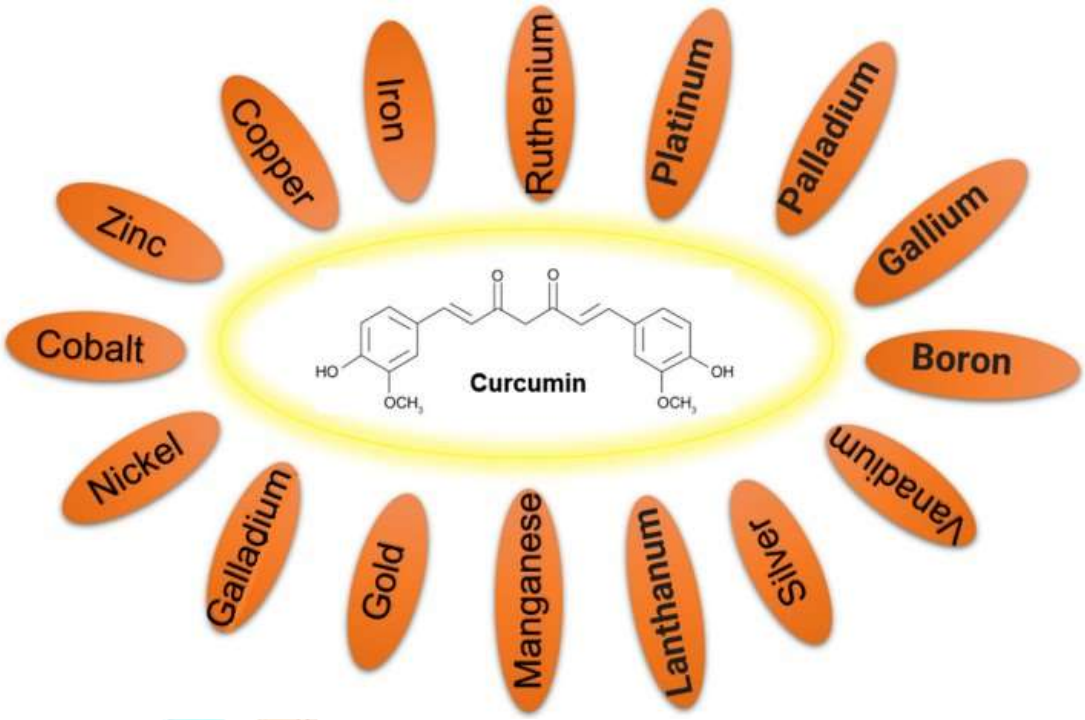

Figure 2. Metal–Curcumin Interactions.

2. 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+}.

3. 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 **(Figure 3)**, 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℃. 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 $La(NO_3)_3{\bullet}6H_2O$ solution (also in ethanol) at pH 6, followed by refluxing at 80℃ [15]. 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℃ until a clear, blood-red solution was obtained [15].

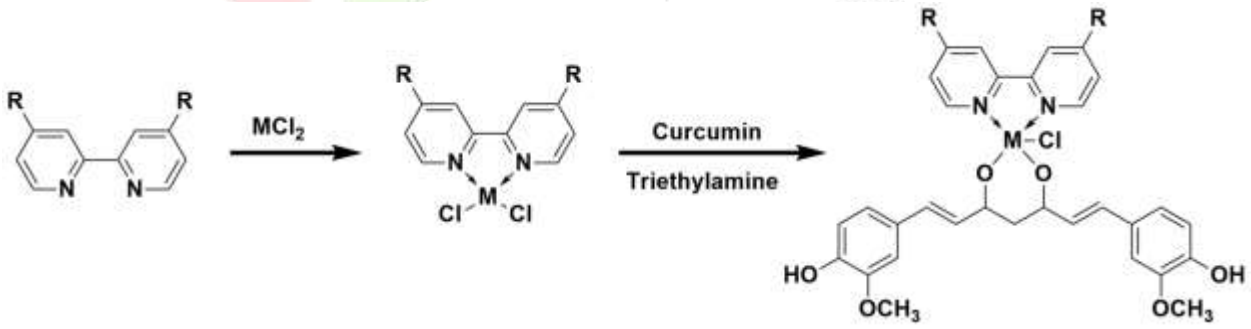

Figure 3. Synthetic route to Curcumin–Metal Complexes.

4. 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 **(Figure 4)**.

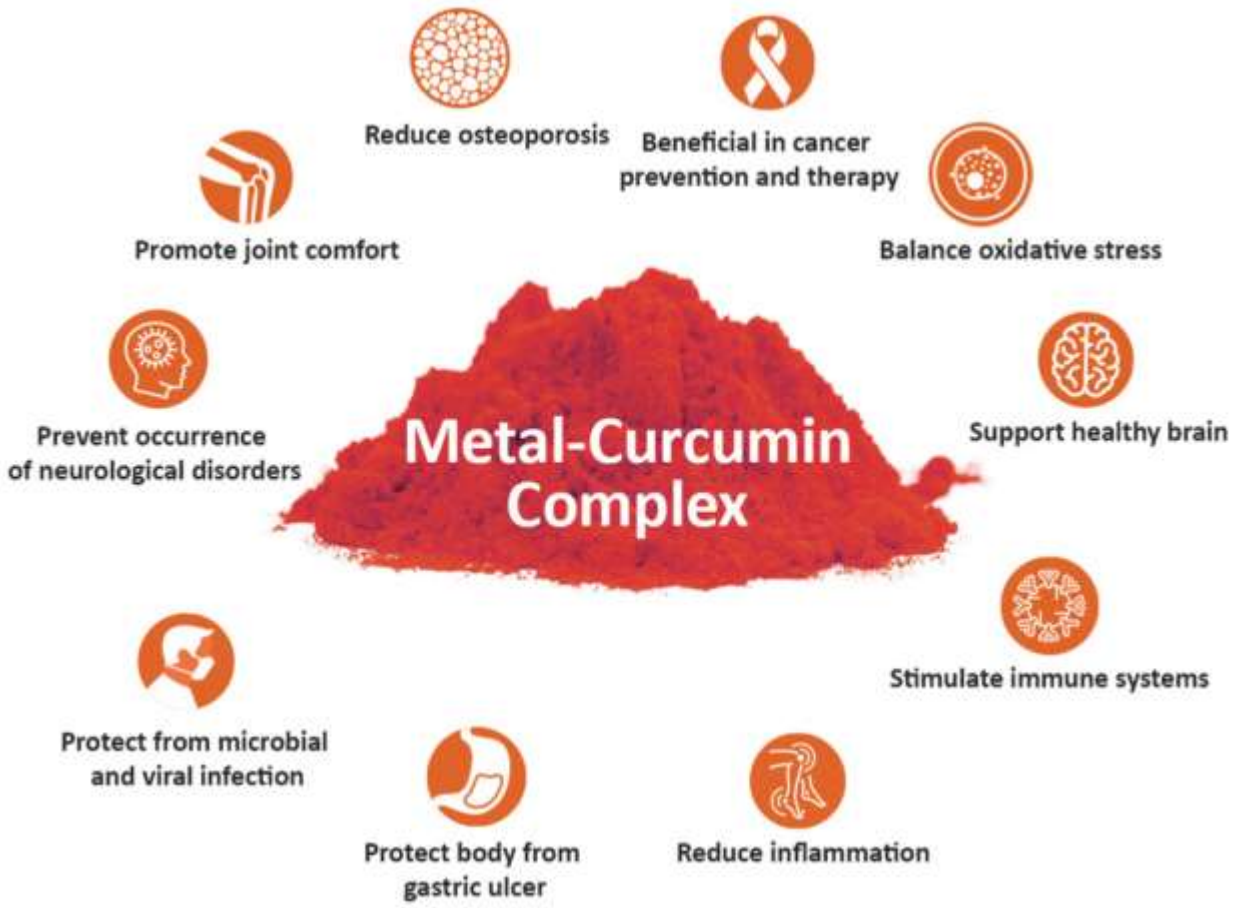

Figure 4. Pharmacological activities of Metal–Curcumin Complex.

4.1. 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 [11] when a superoxide radical attaches to it, which may be one reason why curcumin-metal complexes seem to be more effective antioxidants. 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.

4.2. Anti-Inflammatory

Because it was shown to suppress inflammatory mediators in preclinical and clinical settings, curcumin is widely recognised as an anti-inflammatory drug. Numerous inflammatory cytokines, chemokines, transcription factors, enzymes, and proteases are modulated by curcumin [2,45]. Curcumin has been found to have an improved anti-inflammatory action in metal-curcumin complexes, however. The molecular characteristics of curcumin have been shown to be considerably altered by the binding of metals, which has a considerable impact on the complexes' ability to reduce inflammation.

In vitro and animal models have been used to test the anti-inflammatory effects of a number of metal-curcumin complexes. In one investigation, the biological activities of a complex of Zn^{2+}-curcumin, including its anti-inflammatory action, were identified. Interleukin (IL)-8, transforming growth factor beta-1 (TGF-1) and NF-kappaB (NF-κB) were reported to be inhibited by the Zn^{2+}-curcumin combination when administered to rats [26]. Additionally, oral Zn^{2+}-curcumin therapy reduced the levels of proinflammatory cytokines such tumor necrosis factor-α (TNF-α) and IL-6, and also decreased H^+-K^+-ATPase in the mucosa of rats that had been exposed to alcohol [25]. These findings therefore showed that the Zn^{2+}-curcumin combination blocks a number of inflammatory pathways.

Curcumin-containing compounds of other metals have also been used to reduce inflammation. Strong anti-inflammatory effect has been demonstrated by curcumin-ferrous complexes in experimental animals. A curcumin-iron complex was reported to decrease edema in a rat paw model by 59.76% whereas free curcumin was only able to do so by 51.32%. This impact of the edema reduction is equivalent to that of the common medicine indomethacin, which caused a reduction of 61.76% [46]. It has been demonstrated that a Cu^{2+}-curcumin combination has more biological activity than curcumin by itself. A Cu^{2+}-curcumin complex was discovered to be more effective in modulating the irradiation-induced activation of PKC delta and NF-κB suppression with regard to anti-inflammatory activities [27]. Furthermore, it has been shown that curcumin-Cu^{2+} or -Zn^{2+} complexes reduce cell death by downregulating the NF-κB inflammatory pathway that hydrogen peroxide (H_2O_2) induces in PC12 neuronal cells. These complexes thus have notable neuroprotective properties. In addition to inhibiting the growth of cancer cells, the compound of curcumin and gadolinium (curcumin-PEGylated-$Gd_2(MoO_4)_3$) also suppressed inflammatory indicators. Comparing

this complex to pure curcumin, it demonstrated higher suppression of the inflammatory mediators pIKK, pIKK/, and NF-κB in human pancreatic cancer cell lines. These results imply that the use of curcumin in the production of metal complexes would be beneficial as a nutraceutical for reducing inflammation.

4.3. 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 *Pheretima posthuma*. 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 cells [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.

4.4. Antiviral

The antiviral effects of curcumin are mediated by many mechanisms. It blocks inflammatory molecules, Tat transactivation, HIV protease, integrase, and a number of HIV-associated kinases [45]. In comparison to free curcumin, metal complexed curcumin has demonstrated superior effectiveness against viruses. In comparison to free curcumin, complexes of the central dihydroxy groups of curcumin with boron have been demonstrated to be more effective, as evidenced by a reduction in the IC_{50} value to 6 μM as opposed to values of 100 μM (HIV-1) and 250 μM (HIV-2) with free curcumin. Additionally, curcumin's boron compounds render HIV proteases inactive [36]. A Cu^{2+}-curcumin complex was also shown to have antiviral activity against a variety of viruses, such as respiratory syncytial virus, coxsackie virus B4, reovirus-1, sindbis virus, and punta toro virus, as well as against herpes simplex virus strains, vaccine virus, vesicular stomatitis virus, and coxsackie virus. Except for coxsackie virus B4, vesicular stomatitis virus, and respiratory syncytial virus, which had an antiviral EC_{50} value of 0.08 μg/mL for these specific cell cultures, all viral strains were found to have an antiviral EC_{50} value of 4 μg/mL. Therefore, against a variety of viruses, the Cu^{2+}-curcumin combination exhibits desired antiviral activity [33].

4.5. Cancer

A powerful anticancer substance is said to be curcumin. It fights several cancer kinds as a therapeutic and preventative agent. Due to curcumin's physical restrictions, metal-curcumin compounds have been researched for use in cancer treatments. Researchers have discovered that curcumin-metal complexes with liposomes exhibit greater cellular uptake and ROS formation in cancer cells, resulting in increased cytotoxicity. By enhancing curcumin's stability, encouraging apoptosis, and discouraging angiogenesis and proliferation, Cu^{2+}-curcumin complexes with liposomes have been found to enhance the therapeutic benefits for both primary and metastatic breast cancer [51]. Additionally, the Cu^{2+}-curcumin combination caused DNA photocleavage, photocytotoxicity, and cellular localisation in the cancer cells HeLa and MCF-7. This

compound has extraordinary photodynamic effects since it has demonstrated significant photocytotoxicity with minimal toxicity in the dark [52]. A synthetic curcumin-Cu^{2+} complex's anticancer properties have also been researched. Copper chelates of synthetic curcuminoids were discovered to have increased anticancer action. Additionally, it demonstrated action in extending the lives of animals with ascites tumors and shown a reduction in the amount of solid tumors in mice [53]. In an animal model of triple negative breast cancer, it was discovered that encapsulating the Cu^{2+}-curcumin complex in liposomes improved its anticancer properties without causing any unfavourable side effects [54]. Therefore, curcumin Cu^{2+} complexes improve drug delivery and boost curcumin's therapeutic effectiveness.

It has been demonstrated that a different compound with zinc, ZnO-3-mercaptopropionic acid-curcumin, increases the solubility and delivery of curcumin. Additionally, compared to free curcumin, this compound showed greater cytotoxicity toward breast cancer cells [55]. Additionally, it was discovered that Zn^{2+}-curcumin complexes caused cytotoxicity in neuroblastoma and prostate cancer cell lines [56]. It has been noted that Zn^{2+}-curcumin complexes work in concert to cause apoptosis that is mediated by the mitochondria [57]. In addition to decreasing the survival of cancer cells, Zn^{2+}-curcumin complexes significantly improve cell death responses to therapeutic medicines like doxorubicin *in vitro* and *in vivo*. It has been demonstrated that following internalisation into the cells, this compound degrades and releases curcumin and Zn^{2+} ions [58]. Apoptotic activity in cancer cells was restored by the Zn^{2+}-curcumin complex, which also caused conformational alterations in mutant p53 (R175H and -R273H) proteins. In an orthotopic mouse model, this compound penetrated the blood-tumor barrier, reached the glioblastoma tissues, and resulted in a regression of tumor development [86].

Ru^{2+}-curcumin complexes have also demonstrated a lethal impact at low concentrations in a variety of cancer cell types [87]. When compared to either free curcumin or cisplatin alone, a compound of Ru^{2+}-polypyridyl and curcumin showed greater antiproliferative activity and cytotoxicity against different cancer cells. Through the interaction of the DNA and the inhibition of MEK/ERK signaling, this complex induces apoptosis in cancer cells [59]. When combined with curcumin, another ruthenium(II)-letrozole complex led to the death of cancer cells, most likely via autophagy [60]. Apoptosis is more strongly induced by the Ru^{2+}-curcumin complex than by pure curcumin in colon cancer cells due to the suppression of proteasomes. Additionally, the Ru2+-curcumin combination inhibits isolated proteasomal activity more potently than free curcumin does [61]. A derivative of curcumin (in which the OH groups in curcumin were replaced with OCH_3 groups) was employed to further boost the anticancer activity of Ru^{2+}-curcumin complexes. The anticancer activity of the resultant curcumin derivative Ru^{2+} complex was higher than that of free curcumin [88].

In several cancer cell lines, including HCT-15, SKLU-1, and MCF-7, the compound of Mn2+-curcumin has demonstrated strong cytotoxicity. The Mn^{2+}-curcumin complex was reported to have a lower IC_{50} value than cisplatin and a significantly lower value than free diacetylcurcumin [44]. Thus, a therapeutic potential might be imagined when taking into account the antiproliferative and cytotoxic properties of this complex in human cancer cell lines. It has also been demonstrated that the Co^{3+}-curcumin complex is physiologically more potent against cancer than free curcumin. According to research, the presence of Co^{3+} increases

curcumin's hydrolytic stability, which improves cellular absorption and photo-induced cytotoxicity. In MCF-7 cells, it too has a great photodynamic therapeutic activity, but in the dark, it is considerably less hazardous. According to observations, the released curcumin functions as a phototoxin, generating intracellular ROS that induce cancer cells to die [62]. Co^{3+}-curcumin complexes have been used for their cellular distribution in hypoxic tumor cells because of the high cellular absorption of metal-curcumin complexes, which are liberated by the reduction of metal and function as a cytotoxin [56].

A549 and H1299 non-small-cell lung cancer cell lines have been used to examine the cytotoxic effects of the curcumin and palladium(II) complex. According to research [63], the Pd^{2+}-curcumin combination increases cytotoxic activity and apoptosis relative to the individual agent. Additionally, in human prostate cancer cells, the Pd^{2+}-curcumin combination reduced cell proliferation and triggered apoptosis. In prostate cancer cells, this combination induces Bax, decreases Bcl-2 proteins, phosphorylates JNK, and produces ROS, all of which lead to apoptosis [64]. *In vitro* tests using human colorectal cancer demonstrated a potent antitumor effect for the Pd^{2+} combination with curcumin derivative, which also prevented its spread to the liver. Additionally, it has been demonstrated that this complex inhibits the release of stem cell factor (SCF) and reduces prominin-1 (CD133) molecule expression on tumor cell membranes [65], demonstrating its ability to inhibit the growth of tumours and their ability to metastasize.

Cell cycle arrest, ROS generation, and loss of mitochondrial membrane potential are the key mechanisms through which Ni^{2+}-curcumin complexes exhibit anticancer effects in a variety of cancer cells, including human cervical carcinoma and lung cancer cells [66]. Gallium-curcumin and gallium-diacetylcurcumin complexes have demonstrated cytotoxic effects on bladder, breast, and prostate carcinoma cell lines, suggesting their potential for use in the treatment of cancer [24]. The medicinal effectiveness of curcumin is enhanced by the vanadium complex. Additionally, HeLa and MCF-7 cancer cells significantly responded to this complex's photodynamic treatment under visible light, while experiencing reduced damage at night [72]. Oxovanadium(IV)-curcumin complexes display photocytotoxicity in hepatic HepG2 cancer cells in visible light, in contrast to HeLa cells. This compound triggers the development of ROS in cancer cells, enhances the cellular absorption of curcumin, and induces death in cancer cells [73].

Another compound with phototoxic and apoptosis-inducing properties in cancer cells is platinum-curcumin. Under visible light, this compound was observed to increase cellular ROS and promote apoptotic cell death [67,68]. Additionally, it was shown that this combination sensitised cisplatin-resistant A549/DDP cells and worked synergistically to increase the effectiveness of chemotherapy [69]. It also results in the formation of a platinum-bound DNA adduct and photocytotoxicity in cancer cells when exposed to visible light [70]. The negative effects of other platinum-based treatments are likewise alleviated by the Pt^{2+}-curcumin combination. A study found that the platinum-curcumin complex nanoparticles had improved anticancer efficacy for both *in vitro* and animal models, with less adverse effects. Additionally, it reduced the expression of the molecules vascular endothelial growth factor-2 (VEGFR2) and matrix metalloproteinase-2 (MMP2), which improved its antimetastatic efficacy [71].

Additionally showing anticancer properties, iron oxide nanoparticle formulations of curcumin have also been proven to be nontoxic, bioactive, and anti-inflammatory, and to improve drug delivery to tumors.

These formulations are able to boost human nucleoside transporter genes (DCK, hCNT) and reduce ribonucleotide reductase subunits (RRM1/RRM2), which increases gemcitabine absorption when administered with them. Because iron oxide nanoparticle-curcumin complexes impede the oncogenic CXCR4/CXCL12 signaling pathway and suppress Sonic Hedgehog (SHH) activation, they have an impact on the tumor microenvironment. This combination was demonstrated to promote the accumulation of curcumin in the pancreas in a mouse model, which potentiated the effects of gemcitabine on tumor development and metastasis prevention [74]. Apoptosis was also demonstrated to be induced and breast cancer cell invasion was inhibited by an iron-curcumin combination [75]. Researchers developed a curcumin-loaded nanoparticle with Fe_3O_4 and tested it against leukaemia HL-60 cells because metal produces electromagnetic fields. This formulation, it was discovered, boosted contrast magnetic resonance, leading to elevated apoptosis rates [76]. In order to increase the effectiveness of curcumin in the treatment of cancer, iron complexation may be thought of as a technique.

4.6. Arthritis

For a variety of illnesses and disorders, curcumin has been demonstrated to have excellent effectiveness as a preventative and therapeutic agent. The effectiveness of metal curcumin complexes in comparison to curcumin was then tested against a range of human disorders. A vanadyl-curcumin compound was utilised in a research to treat arthritis. The proliferation of synoviocytes, the expansion of smooth muscle cells, and the development of mice lymphoma cells were all shown to be more effectively reduced by the vanadyl-curcumin complex than by curcumin alone. It can be utilised for the treatment of rheumatoid arthritis since it reduces synoviocyte growth without generating any harm [77]. An animal model of arthritis has been used to study another compound of curcumin and gold. A decrease in paw swelling following 3 weeks of treatment with the gold(I)-curcumin combination (30 mg/kg/day via injection) demonstrated remission in adjuvant-induced polyarthritis. Additionally, this compound improved the structural alterations in the injured rats' limbs [78].

4.7. Osteoporosis

Curcumin metal complexes have also been proven beneficial in treating osteoporosis. The antiosteoporotic properties of curcumin metal complexes have been studied because curcumin inhibits osteoclastogenesis (bone resorption) and suppresses osteoclast-inducing mediators [89]. Some metals, including lanthanide ions, have demonstrated a strong affinity for bone and have been found to prevent the development of osteoclasts. Consequently, a compound of curcumin and lanthanide $Ln(Curc)_3$ was developed as a possible osteoporosis therapy. In an osteoblast-like MG-63 cell line generated from a human osteosarcoma, this complex's antiosteoporotic activity was studied. The lanthanide curcumin complex therapy was reported to have a promising toxicity toward MG-63 cells [79]. The antiosteoporotic potential of a compound containing curcumin and gold nanoparticles was also investigated. It was shown that in bone marrow-derived macrophages, this complex suppresses the osteoclastogenesis triggered by receptor activator of NF-B ligand (RANKL). c-Fos, TRAP, nuclear factor of activated T cells 1 (NFATc1), and osteoclast-associated

receptor (OSCAR) were among the osteoclast development indicators that curcumin-gold nanoparticles suppressed. In addition to *in vitro* studies, the curcumin-gold nanoparticle combination significantly increased bone density and stopped bone resorption in a mouse model of osteoporosis brought on by ovariectomy [80]. In order to prevent and cure osteoporosis, curcumin metal complexes may be helpful.

4.8. Neurological Disorders

Through a series of intricate processes, the nerve system of the brain regulates ideas, memory, movement, and emotions. However, neurological illnesses including Alzheimer's disease, Parkinson's disease, dementia, schizophrenia, and depression may be brought on by genetic disorders, congenital anomalies, infections, lifestyle, environmental factors, and brain damage. Certain neurological conditions are linked to the buildup of amyloid plaques and tau protein aggregates in the neurons. Curcumin has among other natural substances shown positive impacts on brain health via a number of ways. Due to curcumin's potent antioxidant and anti-inflammatory properties, it can protect against neurological illnesses and preserve good brain health. Additionally, curcumin inhibits tau protein, binds to amyloid beta-protein, induces metal chelation, boosts neurogenesis activity, and encourages synaptogenesis [90]. The therapeutic effectiveness of curcumin is nonetheless constrained by its low bioavailability.

Metal ions such Al^{3+}, Mn^{2+}, Fe^{3+}, Cu^{2+}, Pb^{2+}, Hg^{2+}, As^{3+}, and Zn^{2+} may be risk factors for developing neurodegenerative disorders, according to accumulating research [91]. Due to its role in neuronal fibrillation and the development of β-amyloid plaques, the Al^{3+} ion has been demonstrated to be the most detrimental to the brain [92]. Due to curcumin's hydrophobic nature, which allows it to pass the blood-brain barrier, it can effectively chelate the metal ions in the brain and stop metal-induced neurotoxicity. Numerous researches have looked at the usage of metal-curcumin complexes against metal-induced neurotoxicity because of the improved stability and bioavailability of curcumin in these compounds. Gadolinium-curcumin has been found to suppress amyloid plaque aggregation more than free metal or Zn^{2+}-induced analogues [81]. Liu [82] further shown that the Ru^{2+}-curcumin complex has a greater capacity to prevent tau peptide aggregation, presenting a method for developing curcumin-based anti-medications.

Using rat PC12 cells that had been damaged by hydrogen peroxide (H_2O_2) in an *in vitro* investigation, Yan et al. [21] discovered the neuroprotective effects of complexes of curcumin with Cu^{2+} or Zn^{2+}. By boosting the activities of catalase, superoxide dismutase, and glutathione peroxidase and reducing elevated levels of MDA, curcumin-Cu^{2+} or -Zn^{2+} complex systems fight oxidative stress. By inhibiting the NF-κB signaling pathway and enhancing Bcl-2/Bax molecules, these complexes also prevented neuronal cell death. It has been demonstrated that chelated curcumin is substantially more efficient than unchelated curcumin and that the Cu^{2+}-curcumin systems are more protective than the curcumin-Zn^{2+} systems. Therefore, curcumin-Cu^{2+} or -Zn^{2+} complex systems have noteworthy neuroprotective effects [21]. Fe^{3+}-curcumin complexes have the capacity to lessen the buildup of β-amyloid25-35 protein, according to additional *in vivo* investigations carried out on Swiss albino mice. Additionally, mice with the stronger memory showed signs of the Fe^{3+}-curcumin complex. It was discovered that the Fe^{3+}-curcumin combination was more efficient than either curcumin or the Mn^{2+}-curcumin complex [83]. These investigations suggest that metal complexes of

curcumin may open up fresh possibilities for the treatment and preservation of neurological illnesses as well as the preservation of brain health.

4.9. Miscellaneous

Additionally, curcumin-metal complexes are more effective at preventing stomach ulcers than pure curcumin. In one experiment, oral administration of a Zn^{2+}-curcumin complex prevented the development of ulcer ulcers brought on by ethanol, demonstrating gastroprotective efficacy in rats. Additionally, at the same dosages, curcumin-Zn^{2+} complexes more significantly than free curcumin promoted the development of gastric fibroblast cells [25], aiding in the healing of gastric ulcers. The oral administration of a curcumin-Zn^{2+} complex in a rat model decreased stomach volume, gastric lesions, free acidity, total acidity, and pepsin more efficiently than curcumin alone, according to additional investigations [26]. The Zn^{2+}-curcumin combination was more effective than free curcumin since curcumin has been shown to have anti-diabetic benefits when given alone. In one research, a streptozotocin-induced diabetic rat model responded better to oral administration of a Zn^{2+}-curcumin complex than free curcumin in terms of lowering blood sugar levels. Rats treated with Zn^{2+}-curcumin showed improvements in their plasma insulin levels as well as decreases in their blood glucose, lipid profile parameters, and glycosylated haemoglobin (HbA1c). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and urea activity in the blood of diabetic rats were lowered by this compound, demonstrating its nontoxicity [84]. Additionally, studies on Zn^{2+}-curcumin complexes have revealed that they can guard against damage to the reproductive system. In one study, cyclophosphamide-induced increase in oxidative stress in mouse testis was decreased by oral administration of a Zn^{2+}-curcumin complex. It has also been demonstrated that a curcumin-Zn^{2+} complex may reverse the weight loss of the body and reproductive organs caused by cyclophosphamide. By increasing sperm parameters (sperm count, viability, and motility) and lowering serum testosterone, this combination further alleviated reproductive system deficiencies. Compared to curcumin at the same dose, curcumin-Zn^{2+} has demonstrated superior efficacy in treating cyclophosphamide-induced reproductive injury. These findings imply that curcumin-Zn^{2+} are more effective than curcumin alone at preventing reproductive harm [85]. The molecular targets of Metal–Curcumin Complex are illustrated in **Figure 5**.

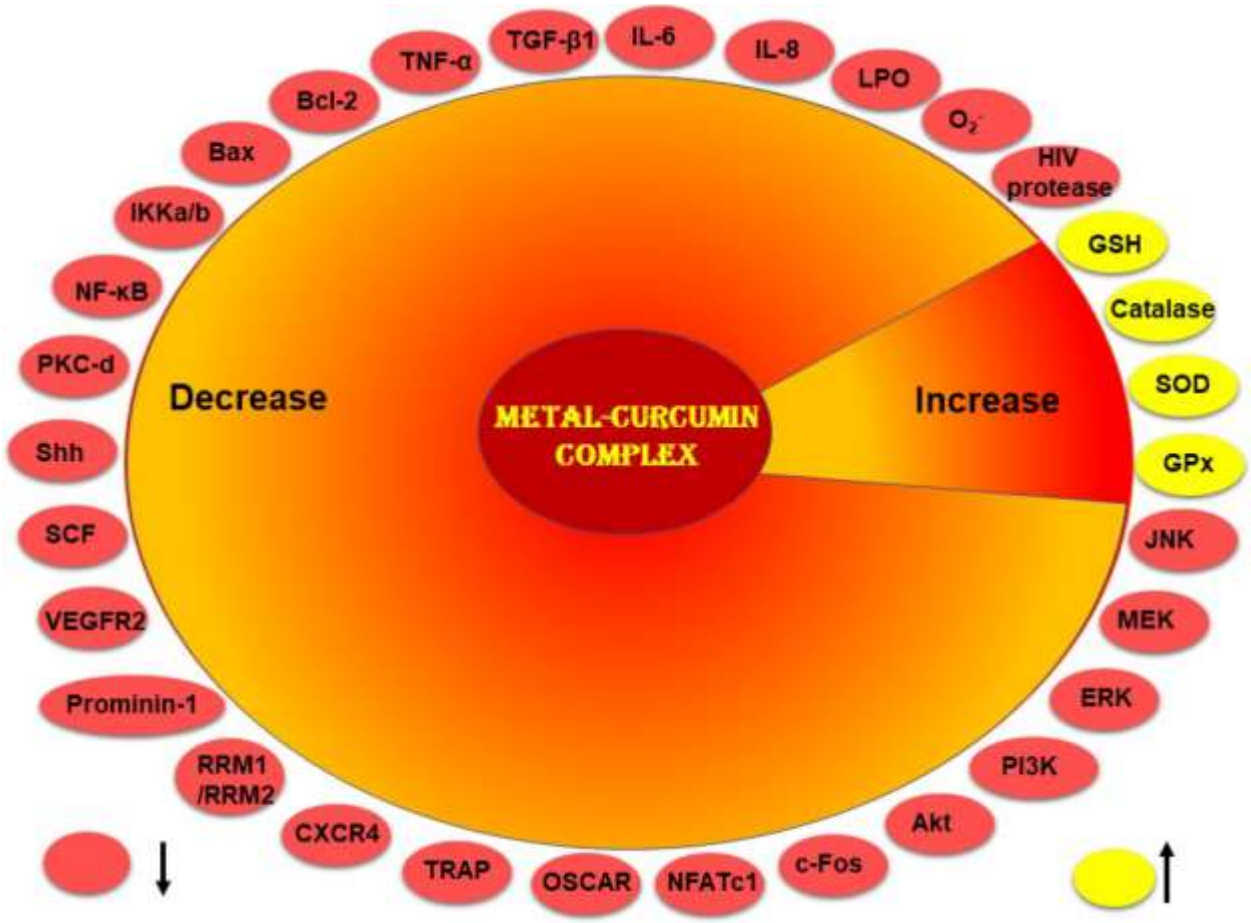

Figure 5. Molecular targets of Metal–Curcumin Complex.

5. Metal–Curcumin Complex applications in Biological Imaging and Radioimaging

Metal-curcumin complexes can be employed in biological imaging and radioimaging since curcumin is a fluorescent chemical. The bioimaging of live cells and tissues is said to be improved by materials with large two-photon absorption cross sections [93]. Curcumin compounds with copper have been studied for biological imaging and radioimaging due to their increased quantum yield and bigger two-photon absorption characteristics. In one investigation, cells were seen using two-photon fluorescence microscopy *in vitro* and *in vivo*. It was discovered that the Cu^{2+}-curcumin complexes have a high capacity for tumor targeting and strong photostability. As a result, it is hypothesised that these complexes may be promising *in vivo* imaging probes and may be helpful in the early identification of tumors [94].

In DMSO-Tris-HCl buffer, Ni^{2+}-curcumin complexes displayed a strong curcumin-based band at about 440 nm. These complexes exhibit significant *in vitro* light-induced cytotoxicity in cancer cells and bind with human serum albumin with a modest affinity [66]. Curcumin palladium complexes have also been demonstrated to be beneficial for fluorescence imaging of cells, which is valuable for analysing how curcumin enters cancer cells and maintains its potential anticancer action [95]. Fluorescence quantum increased when curcumin and the metal gadolinium ion (Gd^{3+}) self-assembled with sodium dodecyl sulphate and HEPES. An improved fluorescence picture was as a result of curcumin's higher cellular absorption [96]. Other complexes, including boron-curcumin and iron-curcumin complexes, have demonstrated higher quantum yields and solution-based photostability. Therefore, these complexes may be suitable for *in vitro* research and medical imaging because to their increased photostability and bigger quantum yields [97].

A boron-curcumin combination was also used in a theranostic modality (RbCur). For this, boron and gadolinium neutron capture treatment was used after the simultaneous delivery of the RbCur complex and gadolinium metal into tumor cells (NCT). Additionally, magnetic resonance imaging (MRI) was done to find out whether tumour cells internalised boron and gadolinium. This combination was useful in determining the cytotoxic activity of curcumin in cancer cells as well as in the detection of drug internalisation [98]. Using magnetic Fe_3O_4 nanoparticles enclosed in a silica shell that contained curcumin, another theranostic investigation was conducted. A combination of microscopy, spectroscopy, and biochemical techniques were used in leukaemia HL-60 cells to carry out the complex's imaging and therapeutic capabilities. Its effectiveness in theranostic regimens was demonstrated by high apoptosis rates and contrast magnetic resonance imaging [76]. Other lanthanide(III) complexes have demonstrated notable visible-light photocytotoxicity in HeLa cells and have also been useful for drug localisation using confocal imaging [99]. Curcumin oxyvanadium(IV) complexes have also demonstrated photocytotoxicity under visible light. Curcumin-oxovanadium complexes have been utilised for cellular imaging because they exhibit green fluorescence [87]. Fluorescence microscopic experiments have also shown that curcumin-oxovanadium complexes have helped in determining the complexes' cellular absorption [73].

6. 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 [113]. 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 [114]. 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 [115], 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.

CONFLICT OF INTEREST

No conflict of interest is declared.

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