AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Curcumin Metallocomplexes: Reexploring Therapeutic Potential of Curcumin

Ravindra B. Laware[1]*, Bhanudas S.Kuchekar[2]

1. Research Scholar, Vinayaka Missions University, Salem, Tamilnadu, India

2. Department of Pharmaceutical Chemistry, MAEER's Maharashtra Institute of Pharmacy, Kothrud, Pune, Maharashtra, India.

ABSTRACT

The natural product curcumin is a polyphenolic compound extracted from the rhizome of *Curcuma longa L*. Curcumin is the principle curcuminoid present in turmeric, responsible for its bright yellow color. Curcumin is a nature's gift to mankind which has broad range of therapeutic, diagnostic and prophylactic potential. In addition to its use as a spice, flavoring and coloring agent in food, turmeric has been used in India for medicinal values for centuries. In Ayurveda, use of curcumin is well documented for the treatment of various ailments. But the applications of curcumin are curtailed by its low solubility, stability, bioavailability, rapid metabolism and short half life. This weapon can be sharpened and re explored as new age one key answer to many ailments and disorders by using it in the form of liposomal, nanoparticulate, microparticulate drug delivery and also by complexing it with metal ions, polymers, cyclodextrine and other carriers. Curcumin has ability to bind with various transition and earth metal ions to form stable complex. Complexation of curcumin with transition metals is one of the useful ways to overcome the problem related to solubility, stability and bioavailability. From several recent studies, it was observed that curcumin metallocomplexes shows greater therapeutic effects than curcumin alone.

Keywords: Curcumin, curcumin metal complex, stability, bioavailability.

*Corresponding Author Email: ravilawre@rediffmail.com

Received 16 April 2015, Accepted 21 April 2015

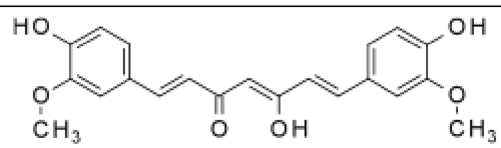
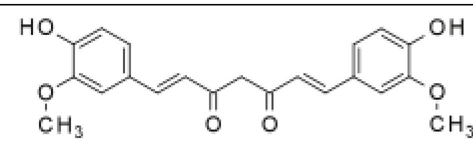
Please cite this article as: Laware RB *et al*., Curcumin Metallocomplexes: Reexploring Therapeutic Potential of Curcumin. American Journal of PharmTech Research 2015.

INTRODUCTION

Curcumin is a diarylheptanoid and principal curcuminoid of turmeric *Curcuma longa L* (Figure 1). In India, it is commonly used as a spice to add color and flavor to the food. In Ayurveda, use of curcumin is well documented for the treatment of various ailments. Recent clinical studies provided scientific evidence for its prophylactic and therapeutic potential. Epidemiological observations are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans. These biological effects of turmeric have been attributed to its constituent curcumin that has been widely studied for its anti-inflammatory, anti-ulcer, anti-oxidant, wound healing, antimalarial and anti-cancer effects. As a result of extensive epidemiological, clinical, and animal studies several molecular mechanisms are emerging that elucidate multiple biological effects of curcumin.

Figure 1: Rhizomes of *C. longa*

In Turmeric, Curcuminoids are the principal coloring agent (6%) of which curcumin amounts 60%, with demethoxycurcumin, bis- demethoxycurcumin forming the rest. Curcumin can exist in several tautomeric forms, including a 1, 3-diketo form and two equivalent enol forms. The enol form is energetically more stable in the solid phase and in solution.[1, 2]

 Enol form of curcumin	 Keto form of curcumin

Uses of curcumin

Curcumin has wide range of therapeutic and prophylactic activities. Curcumin exerts potent anti-inflammatory activity by inhibiting different molecules that play role in inflammation. Studies have proved that curcumin acts as anti ulcer agent. It inhibits growth of Helicobacter pylori, which is responsible for gastric ulcer and cancer. Curcumin is a potent antioxidant as vitamin C, E and Beta carotene thereby exerting it anticarcinogenic, liver protective and anti aging effect. Several clinical studies showed that curcumin inhibits the growth of several types of cancer cells. Curcumin helps to prevent atherosclerosis by reducing the formation of bloods clumps and can prevent myocardial infarct[3]. Two clinical trials investigating curcumin have concluded that the compound may be useful in preventing heart failure and effective against a range of diseases, including cancer and Alzheimer's disease [4, 5]. Curcumin has antimicrobial, antiviral and antifungal actions. Curcumin can chelate with heavy metals such as cadmium and lead, thereby reducing heavy metal toxicity. This property of curcumin explains its protective action to the brain. Research has also confirmed the digestive benefits of turmeric. Turmeric acts as a cholagogue, stimulating bile production, thus, increasing the bodies, ability to digest fats, improving digestion and eliminating toxins from the liver[6]. A recent study has proved that curcumin has antimalarial activity. Curcumin, in addition to having a direct killing effect as an antimalarial, is also able to activate the immune system against *Plasmodium berghei*. Parasite recrudescence and relapse is the major problem associated with P. v*ivax* infection. Studies have proved effectiveness of ARM and curcumin combination to prevent recrudescence and relapse[7, 8]. Figure 2 illustrate the therapeutic applications of curcumin.

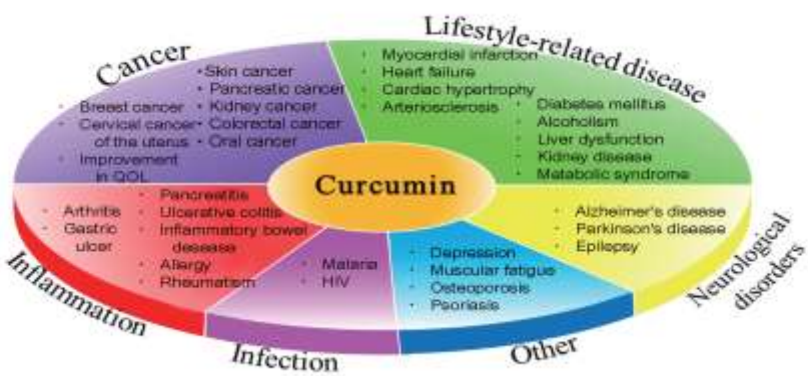


Figure 2: Therapeutic application of curcumin

Structural characteristics of curcumin

Common name of curcumin is diferuloyl methane. It is a symmetric molecule with IUPAC name (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Its chemical formula is $C_{21}H_{20}O_6$, with molecular weight 368.38 and melting point 184^{0}C. It has three chemical entities in its structure: two aromatic ring systems containing o-methoxy phenolic groups, connected by a seven carbon linker consisting of an α,β-unsaturated β-diketone moiety. The diketo group exhibits keto-enol tautomerism and in the crystal state it exists in a cis-enol configuration. The enol form is more stable in many non-polar and some moderately polar solvents than the keto form[9, 10]. The dipole moment of curcumin in the ground state is 10.77 D. It is a hydrophobic molecule with a log P value of ~3.0. It is almost insoluble in water and readily soluble in polar solvents like DMSO, methanol, ethanol, acetonitrile, chloroform, ethyl acetate, etc. It is sparingly soluble in hydrocarbon solvents like cyclohexane and hexane. The absorption spectrum of curcumin has two strong absorption bands, one in the visible region with maximum ranging from 410 to 430 nm and another band in the UV region with maximum at 265 nm region. The molar extinction coefficient of curcumin in methanol is 55,000 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$ at 425 nm[11, 12]

Curcumin reactivity and chemical degradation

Curcumin has three reactive functional groups: one diketone moiety, and two phenolic groups. It is easily degraded in aqueous-organic solutions. It is highly susceptible to pH change. Unlike phenols the degradation of curcumin is found to be through the α, β-unsaturated β-diketo moiety. In aqueous systems at alkaline pH, the acidic phenol group in curcumin donates its hydrogen giving phenolate ion that enables curcumin to dissolve in water. Curcumin chemical degradation results into several products identified as *trans*-6(4'-hydroxy-3'-methoxyphenyl)-2, 4-dioxo-5-hexanal, ferulic aldehyde,ferulic acid, feruloylmethane and vanillin (Figure 3). It is relatively stable below pH 7.0 but with decreasing the pH values, the dissociation equilibrium shifts towards the neutral form having low aqueous solubility[13, 14]. The keto form predominates in acidic and neutral aqueous solutions[15]. The heptadienone linkage between the two methoxy phenyl rings contains a highly activated carbon atom, and the C –H bonds on this carbon are very weak due to delocalization of the unpaired electron on the adjacent oxygens. Hence it acts as an extraordinarily potent H-atom donor at pH 3–7[16]. The enolate form of the heptadienone chain predominates as an electron donor and the mechanism involved is just like scavenging activity of phenolic antioxidants above pH 8[17]. Under acidic conditions, the degradation of curcumin is much slower, with less than 20% of total curcumin decomposed at 1 h[18, 19]. Also Curcumin undergoes much faster degradation when exposed to sunlight. Photodegradation of curcumin results into colorless products as vanillin, ferullic acid, and other small phenols. This photodegradation involves formation of the excited states of curcumin[20, 21].

Bioavailability and metabolism of Curcumin

Phase I clinical trials have shown that curcumin is safe even at high doses (12 g/day) in humans but exhibit poor bioavailability. Major reasons contributing to the low plasma and tissue levels of curcumin appears to be due to poor absorption, rapid metabolism, and rapid systemic elimination. However, studies over the past three decades related to absorption, distribution, metabolism and excretion of curcumin have revealed poor absorption and rapid metabolism of curcumin that severely curtails its bioavailability[22].

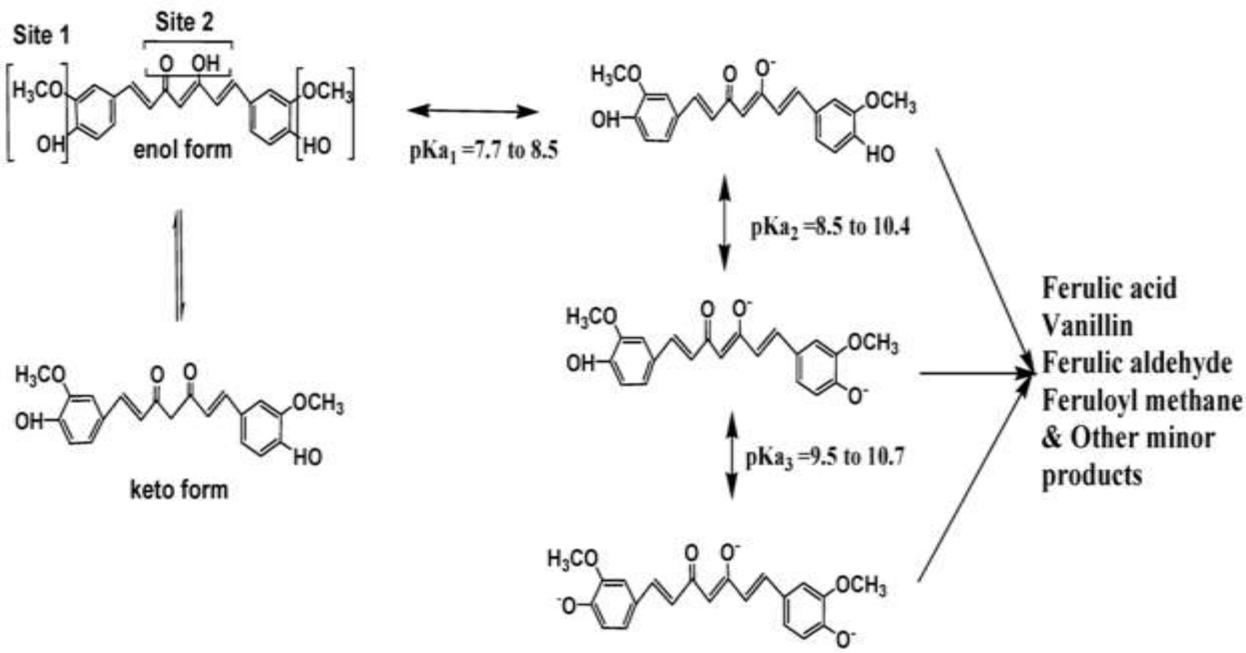


Figure 3: Degradation products of curcumin

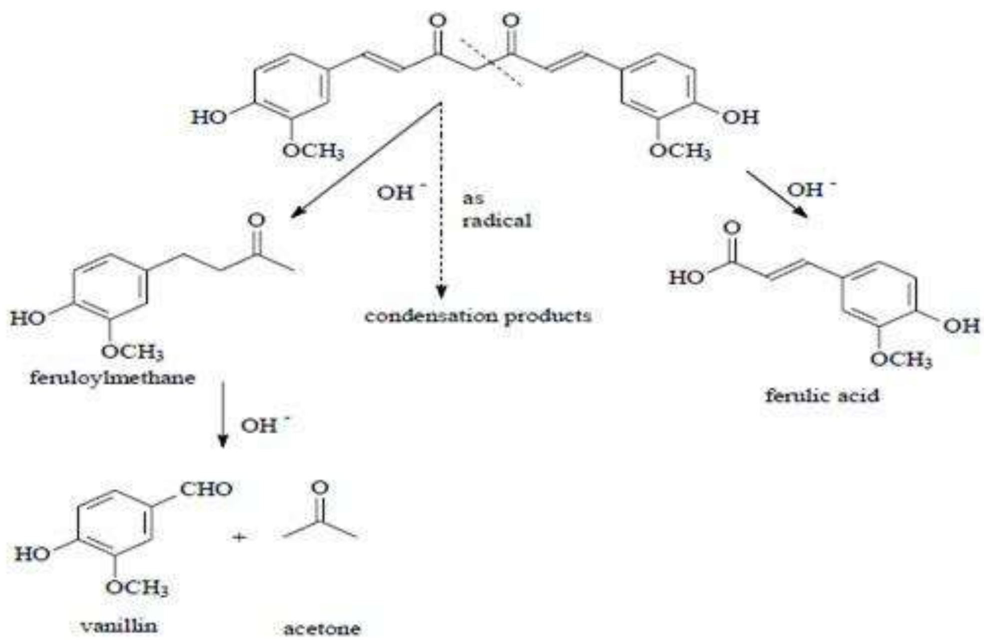


Figure 4: Degradation products of curcumin at basic condition.

Metabolism of curcumin

Various studies have evaluated the metabolism of curcumin in rodents and in humans. It was that absorbed, curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. Liver is the major organ responsible for metabolism of curcumin [23]. It was reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC) in rats. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid. In addition to glucuronides, sulfate conjugates were found in the urine of curcumin treated rats [24]. Hydrolysis of plasma samples with glucuronidase showed that 99% of curcumin in plasma was present as glucuronide conjugates. Curcumin–glucuronoside, dihydrocurcumin–glucuronoside, tetrahydrocurcumin (THC) –glucuronoside, and THC were major metabolites of curcumin found in vivo study (figure 5)[25].

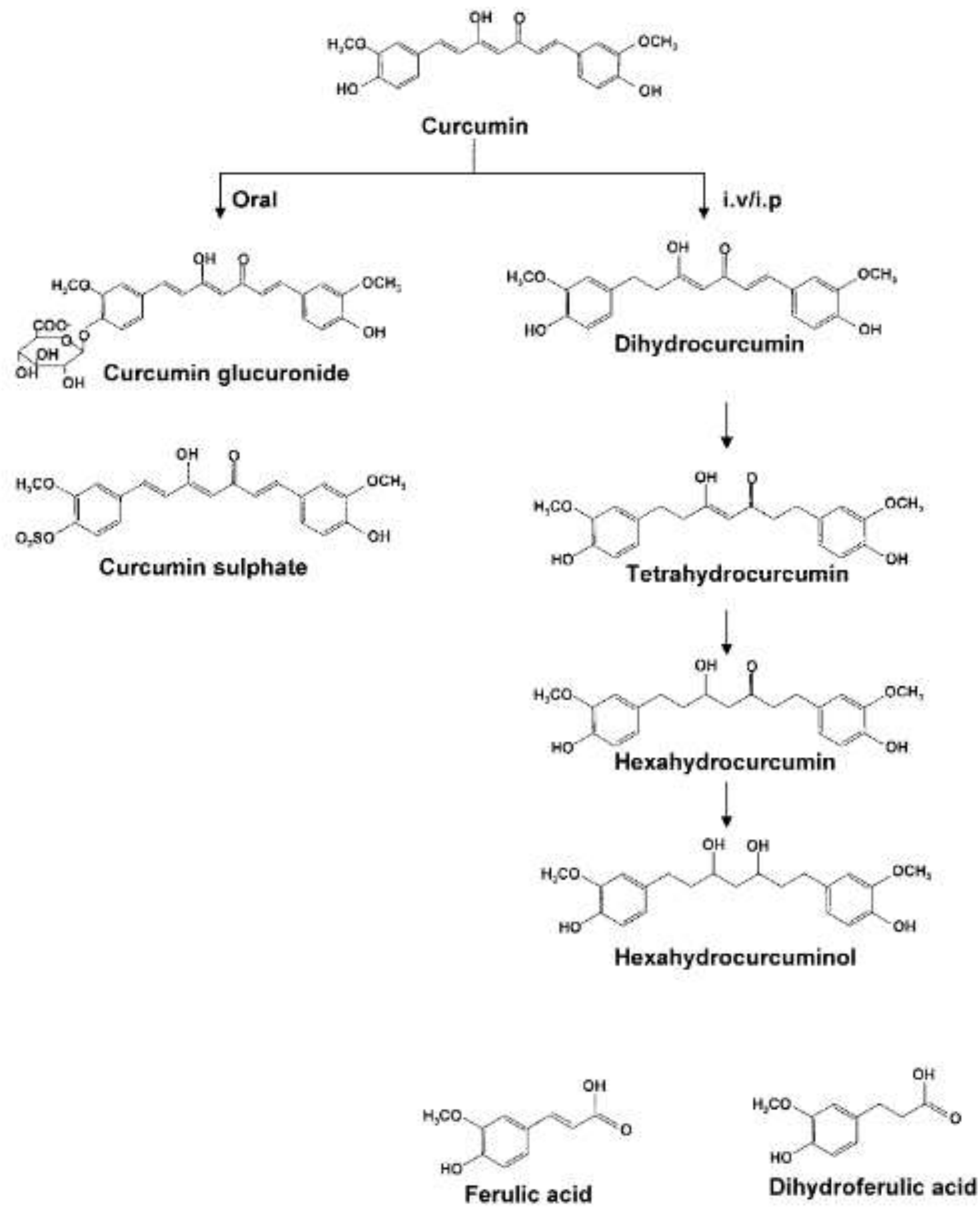


Figure 5: Metabolites of curcumin

Relative biological activity is majorly decided by the systemic elimination of the drug in the body. It was reported that when 1 g/kg curcumin was given orally to rats, 75% of it was excreted in the feces and negligible amounts were found in the urine. A clinical study with 15 patients with oral curcumin doses between 36 and 180 mg of curcumin daily for up to 4 months found neither curcumin nor its metabolites in urine, but curcumin was recovered from feces. The absorption and elimination half-lives of orally administered curcumin (2 g/kg) in rats were reported to be 0.31 ± 0.07 and 1.7 ±0.5 h, respectively [26]. In a research study with radiolabeled curcumin, It was shown that when the drug was administered orally to rats at a dose of 400 mg/rat, nearly 40% of curcumin in unchanged form was found in the feces. Though no detectable amount of curcumin was found in urine, some of the derivatives like curcumin glucuronide and sulfates were observed. The major route of elimination of the radio labeled products was through feces[27].

Approaches to overcome stability and bioavailability problem of curcumin

Several attempts are underway to improve bioavailability of curcumin as enlisted below. These approaches involve the use of adjuvant like piperine that interferes with glucuronidation. Nanoparticles, liposomes, micelles, and phospholipid complexes are other promising novel formulations, which appear to provide longer circulation, better permeability, and resistance to metabolic processes. Complexation of curcumin with transition metals is one of the useful ways to overcome the problems related with solubility, stability and bioavailability. Curcumin can chelate various metal ions to form metallocomplexes of curcumin, which shows greater effects than curcumin alone[28].

1. Adjuvants- Piperine
2. Nanoparticles
3. Liposomes, Micelles and phospholipid complexes
4. Derivatives and Analogues (e.g., EF-24)
5. Complexation of curcumin with transition metals
6. Curcumin-loaded Mesoporous silica nanoparticles
7. Microencapsulation
8. Magnetic nanoparticles of curcumin

Chemistry of curcumin-metal ion interactions

The transition metals are compounds which has an incomplete subshell i.e. Mn[II], Fe[II],Fe[III] etc and due to their instability in structure it has variable oxidation number as well as unstable electronic configuration which modulate the variable redox system. Curcumin has keto’enol form transformation property and utilizing this property in the open chain configuration of enolic form metal ion will attach. This gives a structure of chelates where curcumin will act as ligand (figure 6).

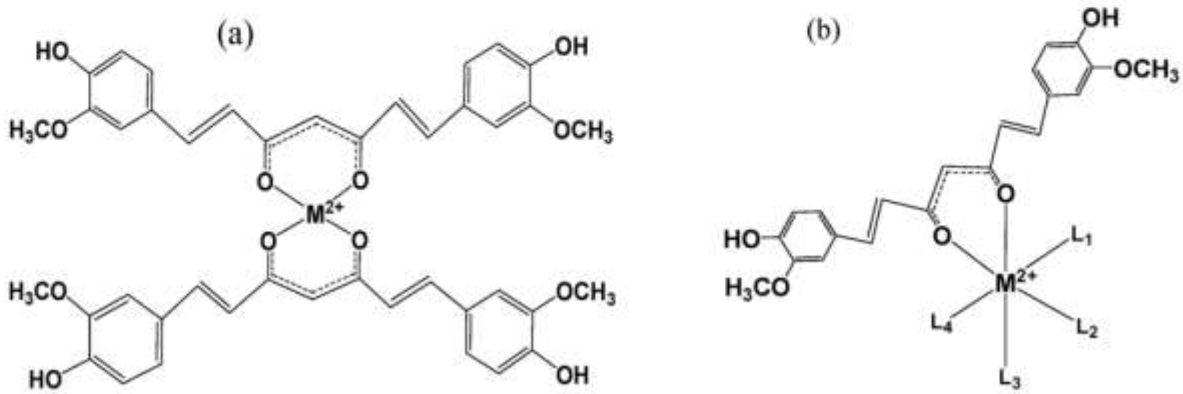


Figure 6: (a) Structure of 2:1 curcumin:metal complex; (b) Mixed ligand curcumin:metal complex.

Curcumin is a monobasic bidentate ligand and forms strong complexes with most of the known metal ions. The α,β-unsaturated β-diketo moiety of curcumin is an excellent chelating agent. Typically, it forms stable structures with 2:1 (ligand: metal) stoichiometry. Rarely 3:1 ligand: metal stoichiometry complexes are observed, e.g., an octahedral complex with Fe3+. The enolic group is responsible for formation of complex, as the enolic proton is replaced by the metal ion while o-methoxy phenolic moiety remains intact in the complexes. The metal-oxygen bond is characterized by IR spectroscopy signals at 455 cm−1 and the carbonyl peaks in the complexes show a small shift of ~10 cm−1 on coordination to metals. Changes in NMR chemical shifts of curcumin have also been reported on metal coordination. Several research studies were conducted on complexes of curcumin with transition metals like Fe3+, Mn2+, Ni2+, Cu2+, Zn2+, Pb2+, Cd2+, Ru3+ and Re3+. Complexes with non-transition metal ions and rare earth ions like Al3+, Ga3+, Sm3+, Eu3+, Dy3+, Y3+, Se2+ and metal oxides like VO2+ have also been synthesized. Stability and reactivity of these metal complexes depend on the nature of the metal ion and stoichiometry of reaction. For synthesis of stable metal complex (2:1), stoichiometric amounts of curcumin and metal salts are dissolved in organic solvent and refluxed for few hours. Precipitate thus obtained is purified by column chromatography or repeated crystallization[28, 29, 30].

Application of curcumin metal complexes

i) Ability of curcumin to form complex with metals reduces toxicity of the metals and some complexes with metals like Cu2+, Mn2+, act as new metal-based antioxidants[31, 32].

ii) Metal toxicity plays prime role in pathology of Alzheimer's disease. It is found that lipophilic curcumin can cross BBB and chelate metals ions that are toxic to neurons. It was observed that people who regularly consume turmeric in their diet are less prone for Alzheimer's disease by forming stable complex with all the metals involved for the pathology. The interaction of curcumin with Al3+ studied extensively with the conclusion that curcumin has ability to reduce development of Al3+ induced Alzheimer's disease[33, 34].

iii) Curcumin Zn complex showed anti cancer, gastroprotective and antidepressant effects in rodent study[35, 36].

iv) Curcumin-gold (Au3+) complex showed *in vivo* antiarthritic activity superior to curcumin[37].

v) Complex of curcumin with vanadyl (VO(Cur)2) 2+ showed antioxidant and anti-rheumatic activity[38].

vi) Curcumin reduces the toxicity of heavy metals like Hg2+, Cd2+, Pb2+ where significant reduction in heavy metal-induced oxidative stress is reported through complex formation[39, 40].

vii) Curcumin-metal complexes showed better anti-tumor activity than curcumin itself. Complexes of curcumin-and 4, 4'-bipyridine with Zn2+ were more effective than curcumin to kill neuroblastoma cells. Curcumin-terpyridyl-lanthanum (La3+) complexes showed enhanced photocytotoxicity in HeLa cells. Bipyridyl-curcumin complexes of Pd2+ inhibit the growth of human prostate cancer cells[41, 42].

viii) Fluorescent curcumin-metal complexes are being explored for imaging of cancer cells. The absorption spectrum of curcumin is altered on complexation with metals. The 1:2 transition metal complexes of curcumin showed a blue shift of the absorption maximum. Re (CO)3(Curcumin)(H2O) complexes are fluorescent and show affinity to beta-amyloid plaques which is being explored in microscopic imaging of the tissue of Alzheimer's disease. 99T (CO) 3(curcumin)(H2O) complexes showed significant affinity to β-amyloid plaques and has potential as novel radiodiagnostic agents for Alzheimer's disease. Complex of curcumin with 68Ga3+ has ability to bind with β-amyloid fibrils very strongly, with possible applications in Alzheimer's disease[43, 44, 45].

ix) Copper-curcumin complex was screened for its antiviral activity and cytotoxicity. Studies revealed that the synthesized compound has good microbicidal activity and would be utilized for the development of vaginal microbicidal gel against viral infections.[46]

x) Curcumin complex with rare earth metals like Sm3+, Eu3+ and Dy3+ showed antibacterial activity[43].

xi) Curcumin-Cu complex was screened as superoxide dismutase mimic. While Zn-curcumin complex was screened for antiulcer activities and found superior to curcumin[47, 48].

xii) Curcumin Zn complex showed increase anticancer activity than curcumin alone[49].

xiii) Complex of Fe-Curcumin was found to possess antitumor activity[50].

xiv) Curcumin-copper complex is being studies for the development of topical contraception prophylaxis[51].

REFERENCES

1. Rangari VD. Pharmacognosy and Phytochemistry. 2nd ed., New Delhi: Career Publication; 2008: 50-52,413-415.
2. Bharat B. Aggarwal CS, Malani N, Haruyo I. Curcumin: The Indian solid gold. Adv Exp Med Biol 2007; 595:1-75.
3. Shimatsu A, Kakeya H, Imaizumi A, Morimoto T, Kanai M, Maeda S. Clinical application of “curcumin”, a multi-functional substance. Anti-Aging Med 2012; 9: 75-83.
4. Aggarwal BB, Surh YJ, Shihsodia S. The molecular targets and therapeutic uses of curcumin in health and disease. Adv Exp Med Biol 2007; 8:595-601.
5. Kanai M, Imaizumi A, Otsuka Y, Hiroki S, Momo H, Kazu T, Shigemi M, Hiroshi I. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol 2012; 69: 65-70.
6. Akram M, Shahab-uddin, Ahmed A, Khan U, Hannan A, Mohiuddin E, Asif M. *Curcuma longa* and curcumin: a review article. Rom J Biol Plant Biol 2010; 2: 65–70.
7. Padmanaban G, Nagaraj VA, Rangarajan PN. Artemisinin-based combination with curcumin adds a new dimension to malaria therapy. Current Sci 2012; 5: 704-711.
8. Patrice NM, Taramelli D, Vivas L. The plant-based immunomodulator curcumin as a potential candidate for the development of an adjunctive therapy for cerebral malaria. Malaria J 2011; 10(1):1-9.
9. Grykiewicz G, Silfirski P. Curucmin and curcuminoids in quest for medicinal status. Acta Biochim Pol 2012; 59: 201–212.
10. Esatbeyoglu T, Huebbe P, Insa MA, DawnChin E, Wagner AE, Rimbach G. Curcumin from molecule to biological function. Angew Chem Int Ed 2012; 51: 5308–5332
11. Gupta S, Prasad S, Ji HK, Patchva S, Webb LJ, Priyadarsini KI, Aggarwal BB. Multitargeting by curcumin as revealed by molecular interaction studies. Nat Prod Rep 2011; 28: 1937–1955.
12. Priyadarsini KI. Chemical and structural features influencing the biological activity of curcumin. Curr Pharm Des 2013; 19; 2093–2100.

13. Kumavat SD, Chaudhari YS, Borole P, Mishra P, Shenghani K, Duvvuri P, Degradation Studies of curcumin. Internal J of Pharm Review Res 2013; 3: 55-61.
14. Gangaitan U, Barman T. Validated method for the estimation of curcumin in turmeric powder. Ind J of trad knowledge 2011; 10: 247-250.
15. Wang YJ, Pan MH, Cheng AL. Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharma Biomed Analysis 1997; 15: 867–876.
16. Jovanovic SV, Steenken S, Boone CW. H-Atom transfer is a preferred antioxidant mechanism of curcumin. J Amer Chem Soc 1999; 21: 677–681.
17. Lin JK, Pan MH, Shiau SYL. Recent studies on the biofunctions and biotransformations of curcumin. Biofactors 2000; 13: 153–158.
18. Tonnesen HH, Karlsen J. Studies on curcumin and curcuminoids:VI –kinetics of curcumin degradation in aqueous solution. Eur Food Res Tech 1985; 180: 402–404.
19. Tonnesen HH, Karlsen J, Van Henegouwen GB. Studies on curcumin and curcuminoids: VIII –photochemical stability of curcumin. Eur Food Res Tech 1986; 183:116–122.
20. Priyadarsini KI, Photophysics, Photochemistry and Photobiology of Curcumin: Studies from organic solutions, bio-mimetics and living cells. J Photochem Photobiol 2009; 10: 81–96.
21. Khurana A, Ho CT. High Performance Liquid Chromatographic Analysis of Curcuminoids and Their Photo-oxidative Decomposition Compounds in *Curcuma longa*. J Liquid Chromatogr 1988; 11: 2295–2304.
22. Preetha A, Kunnumakkara AB, Robert AN, Aggarwal BB. Bioavailability of Curcumin: problems and promises, Mol Pharmaceutics 2007; 6: 807-818.
23. Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, Steward WP, Gescher AJ, Berry DP, Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. Br J Cancer 2004; 90: 1011–1015.
24. Holder GM, Plummer JL, Ryan AJ, The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. Xenobiotica 1978; 8: 761–768.
25. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug Metab Dispos 1999; 27: 486–494.
26. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, Pirmohamed M, Marnett LJ, Gescher AJ, Steward WP. Pharmacodynamic and pharmacokinetic study of

oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res 2001; 7: 1894–1900.

27. Ravindranath V, Chandrasekhara N. Metabolism of curcumin studies with [3H]curcumin. Toxicology 1981; 22: 337–344.
28. Priyadarsini KI. The Chemistry of curcumin: from extraction to therapeutic agent. Molecules 2014; 19: 20091-20112.
29. Bagchi A, Semwal A, Kaur N, Jassal M., Mukherjee P. Curcumin and Curcumin metal complex: Ancient weapon new targets. Univ J of Pharm 2013; 2: 8-19.
30. Subhan MA, Alam K, Rahaman MS, M. A. Rahman A, Awal MR. Synthesis and characterization of metal complexes containing curcumin (C21H20O6) and study of their anti-microbial activities and dna binding properties, J Sci Res 2014; 6: 97-109.
31. Vajragupta O, Boonchoong P, Berliner LJ. Manganese complexes of curcumin nanlogues: Evaluation of hydroxyl radical scavenging ability, superoxide dismutase activity and stability towards hydrolysis. Free Radic Res 2004; 38: 303–314.
32. Barik A, Mishra B, Shen L, Mohan H, Kadam RM, Dutta S, Zhang H, Priyadarsini KI. Evaluation of new copper–curcumin complex as superoxide dismutase mimic and its free radical reactions. Free Radic Biol Med 2005; 39: 811–822.
33. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer’s disease animal models. J Alzheimer’s Dis 2004; 6: 367–377.
34. Jiang T, Zhi X, Zhang Y, Pan L, Zhou P. Inhibitory effect of curcumin on the Al(III)-induced A beta(42) aggregation and neurotoxicity in vitro. Biochim Biophys Acta Mol Basis Dis 2012; 1822: 1207–1215.
35. Pucci D, Bellini T, Crispini A, D’Agnano I, Liquori PF, Garcia-Orduna P, Pirillo S, Valentini A, Zanchetta G. DNA binding and cytotoxicity of fluorescent curcumin-based Zn(II) Complexes. Med Chem Commun 2012; 3: 462–468.
36. Mei X, Xu D, Xu S, Zheng Y, Xu S. Gastroprotective and antidepressant effects of a new zinc(II)-curcumin complex in rodent models of gastric ulcer and depression induced by stresses. Pharmacol Biochem Behav 2011; 99: 66–74.
37. Sharma KK, Chandra S, Basu DK. Synthesis and antiarthritic study of a new orally active diferuloyl methane (curcumin) gold complex. Inorg Chim Acta 1987; 135: 47–48.
38. Thompson KH, Bohmerle K, Polishchuk E, Martins C, Toleikis P, Tse J, Yuen V, McNeill JH, Orvig C. Complementary inhibition of synoviocyte, smooth muscle cell or mouse

lymphoma cell proliferation by a vanadyl curcumin complex compared to curcumin alone. J Inorg Biochem 2004; 98: 2063–2070.

39. Oguzturk H, Ciftci O, Aydin M, Timurkaan N. Beytur A, Yilmaz F. Ameliorative effects of curcumin against acute cadmium toxicity on male reproductive system in rats. Andrologia 2012; 44: 243–249.
40. Agarwal R, Goel SK, Behari JR. Detoxification and antioxidant effects of curcumin in rats experimentally exposed to mercury. J Appl Toxicol 2010; 30: 457–468.
41. John VD, Kuttan G, Krishnankutty K. Anti-tumor studies of metal chelates of synthetic curcuminoids. J Exp Clin Cancer Res 2002; 21: 219–224.
42. Lou JR, Zhang XX, Zheng J, Ding WQ. Transient metals enhance cytotoxicity of curcumin: Potential involvement of the NF-kappaB and mTOR signaling pathways. Anticancer Res 2010; 30: 3249–3255.
43. Song YM, Xu JP, Ding L, Hou Q, Liu JW, Zhu ZL. Syntheses, characterisation and biological activities of rare earth metal complexes with curcumin and 1,10-phenanthroline-5,6-dione. J Inorg Biochem 2009; 103: 396–400.
44. Sagnou M, Benaki D, Triantis C, Tsotakos T, Psycharis V, Raptopoulou CP, Pirmettis I, Papadopoulos M, Pelecanou M. Curcumin as the OO bidentate ligand in “2+1” complexes with the [M(CO)3]+ (M = Re, Tc99m) tricarbonyl core for radiodiagnostic applications. Inorg Chem 2011; 50: 1295–1303.
45. Asti M, Ferrari E, Groci S, Atti G, Rubagotti S, Lori M, Capponi PC, Zerbini A, Saladini M, Versari A. Synthesis and characterization of 68Ga-labeled curcumin and curcuminoid Complexes as potential radiotracers for imaging of cancer and Alzheimer’s disease. Inorg Chem 2014; 53: 4922–4933.
46. Chauhan G, Rath G, Goyal AK. *In vitro* anti-viral screening and cytotoxicity evaluation of copper-curcumin complex. Artif Cells Nanomed Biotechnol 2013;41:276-281.
47. Barik A, Mishra B, Shen L. Evaluation of a new copper(II)-curcumin complex as superoxide dismutase mimic and its free radical reactions. Free Radical Bio Med 2005; 39: 811–822.
48. Mei X,, Xu D, Xu S, Zheng Y. Novel role of Zn(II)-curcumin in enhancing cell proliferation and adjusting proinflammatory cytokine-mediated oxidative damage of ethanol-induced acute gastric ulcers. Chemico Biological Interactions 2012;197: 31–39.
49. Modi G. Increased anticancer activity of curcumin-Zn (II) complex by species sensitive method. Der Chemica Sinica 2011; 2 (1): 91-99.

50. Khalil MI, Al-Zahem AM, Al-Qunaibit MH. Synthesis, characterization, Mössbauer parameters, and antitumor activity of Fe(III) curcumin complex, Bioinorg Chem Applications 2013; 1:1-5.
51. Gaurav C, Goutam R, Rohan KN, Sweta KT, Abhay CS, Amit GK. (Copper-curcumin) β-cyclodextrin vaginal gel: delivering a novel metal-herbal approach for the development of topical contraception prophylaxis. Eur J Pharm Sci 2014; 18:183-191
52. Zebib B, Mouloungui Z, Noirot V. Stabilization of curcumin by complexation with divalent cations in glycerol/water system. Bioinorg Chem Applications 2010;1: 1-8

AJPTR is

- **Peer-reviewed**
- **bimonthly**
- **Rapid publication**

Submit your manuscript at: editor@ajptr.com