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Studies on Metal Chelating Property and Pharmaceutical Applications of Curcumin Metal Complex.

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I. Introdution

1.1 Curcumin

"From kitchen to clinic" Curcumin plays a vital role in human life. Curcumin (=1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a component of the Indian spice turmeric, manufactured from the rhizome of the perennial herb Curcuma longa that is widely cultivated in tropical countries in South and South East Asia, especially in China and India. Curcuma longa belongs to the Zingiberaceae (ginger) family[1-5].The structure of curcumin ($C_{21}H_{20}O_6$) was first described in 1913 by Lampe and Milobedeska and shown to be feruloylmethane (Aggarwal et al., 2003). Curcumin (=CurcH) is the major component of three curcuminoids that give turmeric its characteristic yellow color and is used as a food colorant, flavoring and additive (Figure 1-2). The minor curcuminoid components are demethoxycurcumin (=DMCurcH) and bis-demethoxycurcumin (=BDMCurcH) in which one or both –OMe functionalities at the outer phenol rings are removed.

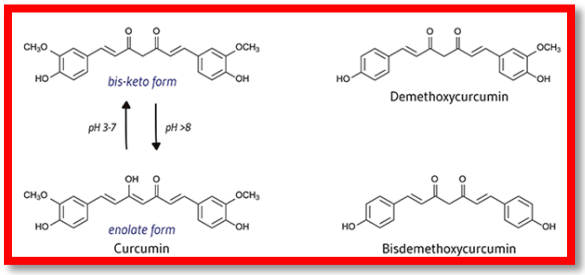
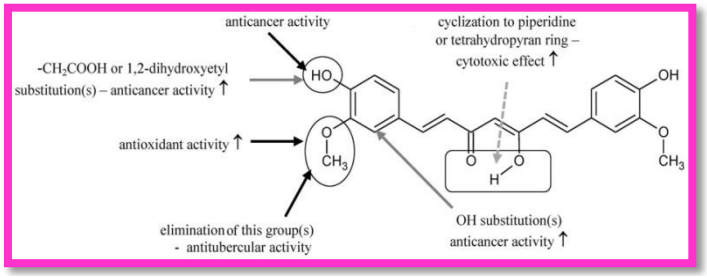


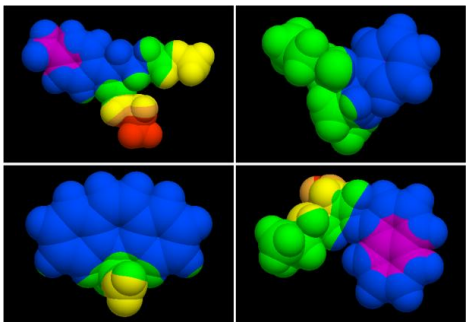
Figure 1.1 Keto enol tautomers of curcumin

1.2 Molecular target and chelating ligand effect of curcumin

Various studies have shown that curcumin modulates numerous targets (Figure). These include the growth factors, growth factor receptors, transcription factors,cytokines, enzymes, and genes regulating apoptosis.The chemical structure of curcumin was first identified in 1910 by Miłobędzka, von Kostanecki and LampeThrough chemical derivatization, It was clearly established the identity of curcumin as diferuloylmethane or 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.The two potentially useful derivatives, dicarbomethoxycurcumin and dicarboethoxycurcumin, by treatment of curcumin with two equivalents of methyl- or ethylchloroformate, respectively, in the presence of aqueous potassium hydroxide. These two derivatives are particularly valuable in curcumin chemistry as they are easily accessible in good yields and high purity[6-8].



1.3 Molecular targetand chelating ligand effect of curcumin



1.4Molecular targetand chelating ligand 3D effect of curcumin

II. Materials and Methods

2.1 Synthesis of Curcumin Fresh rhizomes were cleaned, washed with deionized water, sliced and dried in the sun for one week and again dried at 50 °C in a hot air oven for 6 hours. Dried rhizomes were cut in small pieces, powdered. Approximately 20g of sample were taken and set up with various solvent from nonpolar to polar. 150mL of solvent was added and extracted according to their boiling point for 6 hours. The solvents used were Hexane (b.pt = 69° C), Chloroform (B.P = 61°C), Ethyl acetate (b.pt=77°C), Methanol (b.pt=65°C), and Acetone (b.pt=56.53°C). And one sample was extracted with hexane for 2 hours and hexane extract was discarded and the powder was re-extracted with methanol for 6 hours. After completion of extraction the dark brown extract was then cooled, filtered, concentrated using rotary evaporator, and finally by vacuum suction to get a crude dried extract which was black orange in color. Each raw sample of turmeric was extracted by the same method and yield was calculated.Curcuma longa (Turmeric) rhizome were collected from Assam - Lakhadong variety. All solvents / Chemicals used were of AR / HPLC grade and obtained from E-Merck. The reference standard of Curcumin was purchased from Sigma Chemicals Co. U.S.A[9-11].

2.2 Synthesis of Curcumin- Chromium complex

The Cr(III)–curcumin complex was synthesized by mixing equi-molar amounts of Chromium chloride (1.0 mmol) and curcumin (0.37 g, 10 mmol) in ethanol and the mixture was heated at 60°C for 1 h under a nitrogen atmosphere and the reaction was further continued for 2h under reflux. Then the complex solution formed was concentrated and the solid residue was separated by filtration and washed several times by water/ethanol to remove unreacted curcumin.

2.3 FTIR IR spectra of curcumin and its complexes were recorded on spectrometer in KBr discs with resolution of4 cm-1 and scans of 32. The spectral range was from 4000 to400 cm-1.

Electronic spectra

Electronic spectra of the ligands and their complexes were recorded in DMSO on a Thermo electron Nicolet evolution 300 UV-vis spectrophotometer.

2.4 Antimicrobial Activity of Compound on Pathogens -Well Diffusion Method Antimicrobial activity of the extract of compound was determined using well diffusion method. It was performed by sterilizing Mueller Hinton agar media. After solidification, wells were cut on the Mueller Hinton agar using corn borer. The test pathogens were swabbed onto the surface of Mueller Hinton agar plates. Wells were impregnated with 25 µl of the test samples. The plates were incubated for 30 min to allow the extract to diffuse into the medium. The plates were incubated at 30^{o}C for 24 hours, and then the diameters of the zone of inhibition were measured in millimeters. Each antimicrobial assay was performed in triplicate and mean values were reported.

III. Results And Discussion

In order to establish the relativeimportance of phenolic and enolic centre to the antimicrobial activity of curcumin,the synthesis of only 1:1 complexes were attempted even though 1:2 complexes ofcurcumin were also reported [12-13]. This was to retain the number of phenolic group as two, similar to the parent curcumin.

Curcumin

Electronic spectra

UV spectrum was recorded in the range of 300-600 nm in DMSO. Maximum absorption band of curcumin was obtained at 438 nm indicating the n- Pi* transition. Figure 4.1 showed the electronic spectra of curcumin.

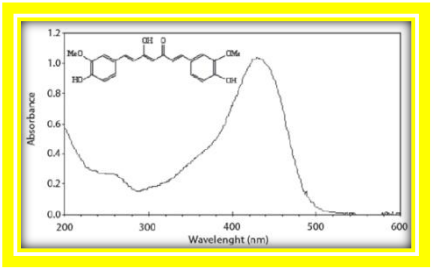


Figure 4.1 Electronic spectra of curcumin

Infrared spectra

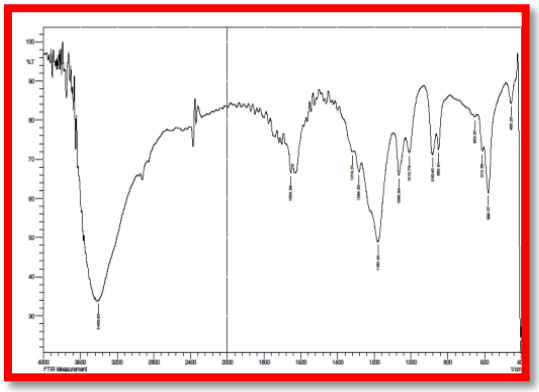


Figure 4.2IR spectra of curcumin

The strong broad absorption band centred at 3440 cm-1 was interpreted as the result of (O-H) stretching. The peak at 2930 cm-1 is characteristic to C-H). The sharp band at 1628 cm-1 can be assigned to (C=O). The intense band at 1500 cm-1 may be due to (C=C).The sharp peak at 1271 cm-1 corresponds to (C-O) of phenol. A medium intense band at 1029 cm-1 can be ascribed to (O-CH3). The spectrum obtained was as in **Fig 4.2.**

Curcumin - metal complex

The UV spectra of curcumin-I exhibited apeak at 434 nm and in metal complex the absorption maxima was shifted tohigher region of 437-442 nm. The complex exhibited a shoulder peak in therange of (450-463 nm) indicating Curcumin Metal (M^{3+}) charge transfertransition. The absorption data obtained was in agreement with the data for 1:1complexes as suggested by Barik et al [13-16]. For 1:2 complex Barik et al showed anabsorption in the range of 370 nm. Curcumin exhibit keto-enol tautomerism, theenol form that predominate in basic condition easily gets deprotonated to giveenolate ion, which is capable of forming very stable complex with a vast range ofmetal ion . In acidic condition the diketone form predominate whichcan also undergo metal chelation. The strong C=O stretching peak observed forcurcumin at 1623 cm^{-1} showed a blue shift in metal complex and the valueassigned is 1606 cm-1Cr(III) complex. The IR data of the entire synthesized complexsuggest the chelation mode as shown in **Fig. 4.4,** where the ionic enol form is chelated with metal.In the IRspectrum of curcumin and its metal complexes the O-H band of phenol do notshow considerable shift from 3433 cm-1 hence concluded that the phenolic O-H isnot involved in complex formation.Moreover, theappearance of new bands at 506 cm^{-1} corresponds to ν(M-O). Also the new bands at 1380cm^{-1} and 1282 cm^{-1} corresponds to symmetric and asymmetric stretching for ν(M-O) which evidenced the participation ofthe COO- ion in the complexes. These facts are further supported by the appearance of bands between 1390-1456 cm^{-1} and1280-1321cm^{-1} attributed to υasy(COO-) and υsy(COO-).

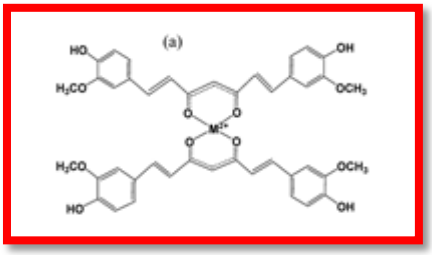


Figure 4.3 curcumin - Cr metal complex

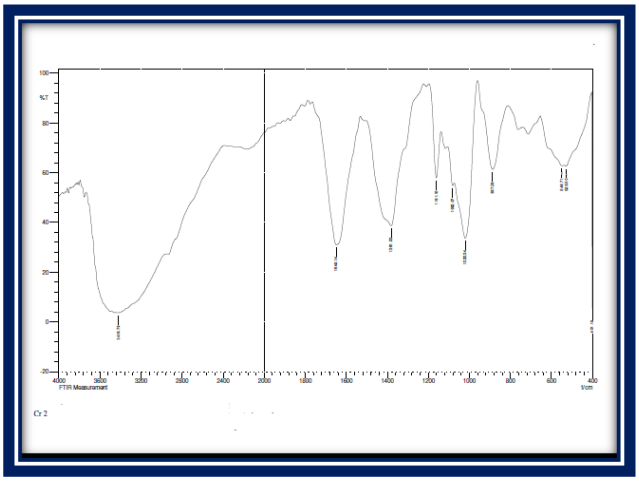


Figure 4.4 IR spectra of curcumin - Cr metal complex

2.5.3.4 Thermal Analysis

TGA was used to determine degradation temperatures and absorbedmoisture content. Curcumin was stable up to 150^{o} C and the DTG peak observed at160^{o} C can be attributed to the dehydroxylation of two -OH groups and after 400^{o} Cthere is complete decomposition [12-14]. The Cr III complex showed a weight lossaround 175^{0}C corresponding to loss of coordinated water (weight loss found:3.7%, calcd 3.8%). The Cr(III) complex showed a weight loss at 165^{0} C due to loss of coordinated water (weight loss found: 3.8%, calcd 4.0%).

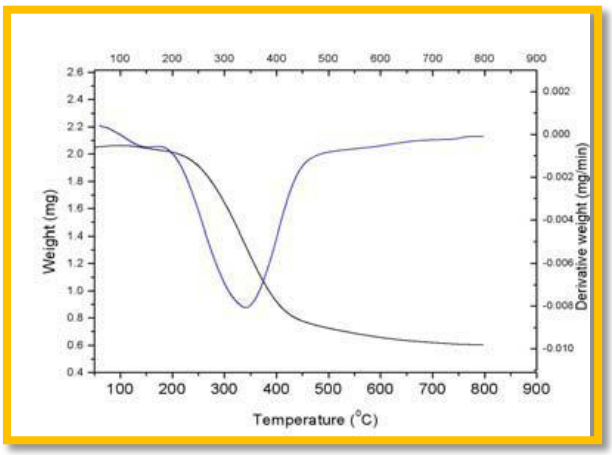


Figure 4.5 TGACurve of curcumin

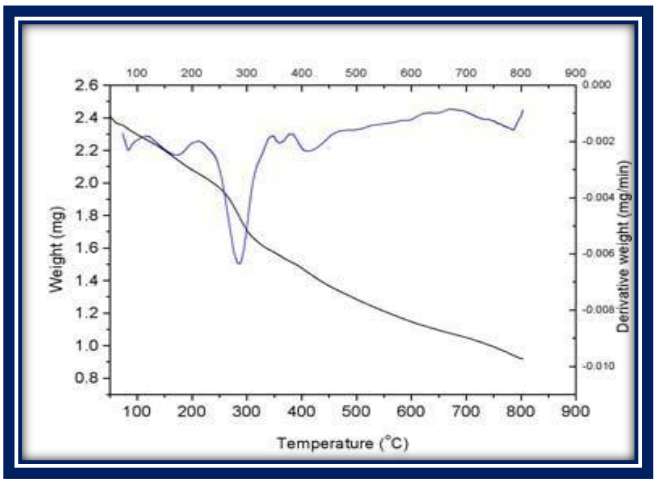


Figure 4.6 TGA curve of curcumin metal complex

Antimicrobial activity of the compound against bacterial pathogens

Pharmaceutical applications of Cr-Curcumin complex was studied for Staphylococcus aureus, E. coli, Klebsiella pneumonia and Pseudomonas fluorescence.On the basis of MCI zone area the activity of the complex is in the order, Klebsiella pneumonia> E. coli > Staphylococcus aureus> Pseudomonas fluorescence**.**The following figures (1-4)showed the antimicrobial activity for the microbes.

Plate: 1.complexagainst Staphylococcusaureus

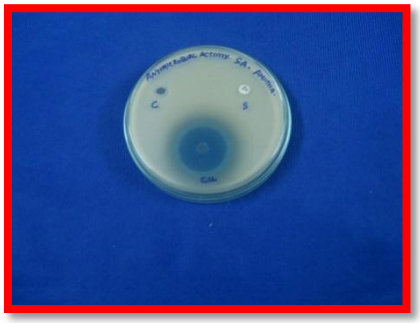


Plate: 2. complex against E.coli

Plate: 3. complex against Klebsiella pneumonia

Plate: 4. complex against Pseudomonasfluorescence

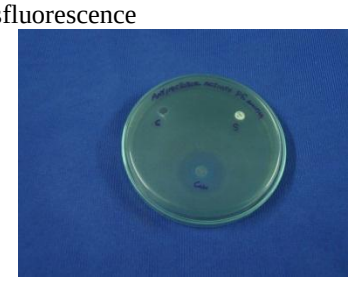


Table: 4.1. Antimicrobial activity of the compounds against microbial pathogens

Test organisms	Cr	Solvent control	Standard Amp 10µg
Staphylococcus aureus	40	NZ	16
E. coli	43	NZ	14
Klebsiella pneumonia	47	NZ	23
Pseudomonas fluorescence	32	NZ	19

Solvent used : DMSO (Dimethyl Sulphoxide)
Standard used: Ampicillin 10 µg.

IV. Conclusion

The novel Cr-Curcumin complex was synthesized and its structure was confirmed by FT-IR spectra.The interaction of curcumin and Cr(III)was the significant Cr(curcumin)$_2$. The diffuse reflectance IR spectra indicated that the complex was reasonably stable both in aqueous solution and in solid state.Pharmaceutical applications of Cr-Curcumin complex was studied for Staphylococcus aureus, E. coli, Klebsiella pneumonia and Pseudomonas fluorescence.On the basis of MCI zone area the activity of the complex is in the order, Klebsiella pneumonia> E. coli > Staphylococcus aureus> Pseudomonas fluorescence**.** Resultsobtained provide a promising role of Chromium- curcumin complexes in diverse biological applications especially for UTI patients. It is simple to prepare and cost-effective drug for patients.In the complex of curcumin the enolate form of curcumin ligands to the metal. The complexes have comparableantimicrobial activity to parent curcumin-I, establishing the minimal involvement ofketo-enol moiety of curcumin as the antioxidant centre and hold up the phenolic -OH as the prime centre for the antioxidant activity. Thus it can concludethat different parts of curcumin help in different way to accelerate its biologicalproperty. The C=O group as metal chelator reducing oxidative stress, phenol asantioxidant centre and neutral hydrophobic conjugated hydrocarbon bridgefacilitate the penetration into the microbes-cell barrier.

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