CHAPTER 1

GENERAL INTRODUCTION
1,3-DIKETONES AND THEIR METAL COMPLEXES

One of the fascinating features of modern coordination chemistry is the ever increasing academic, commercial and biological interest exhibited by metal complexes of organic molecules, both natural and synthetic.$^{1,2}$ This is mainly because of the ability of coordinated metal atom/ion to influence the structure, properties and applications of the organic compound. Thus numerous highly efficient catalytic systems based on metal complexes for the synthesis and manufacture of several industrial chemicals are available. Similarly, several synthetic metal complexes which mimic the behaviour of complex biomolecules are known and at present the study of such compounds are receiving much attention.$^{3,4}$ Although the results obtained so far do not always parallel those in nature, a knowledge of the chemistry is being built up and the biochemical role of metal ions in natural ligand systems is beginning to be better understood.$^{5}$

The structure, properties and uses of metal complexes are dependent both on the nature of the metal ion and the type of the ligands coordinated. Thousands of new ligand systems have been developed in recent years because of the developments in modern synthetic organic chemistry. This trend is evident from the reports on numerous compounds based on 1,3-diketones and related compounds.
The 1,3-diketones have several interesting structural features. They serve as the best example of keto-enol tautomerism and intramolecular hydrogen bonding. For a coordination chemist, perhaps the most important aspect of β-diketones is their ability to form diverse types of complexes with various metal and metalloid elements. The 1,3-diketones still serves as the starting material for the design and synthesis of a large number of compounds having wide application in many fields. Therefore, investigation on metal complexes of different types of 1,3-diketones have considerable importance. The present investigation is mainly on certain structural and biological aspects of a series of 'unsaturated' 1,3-diketones and their metal complexes. Therefore, some of the salient features of 1,3-diketones and metal 1,3-diketonates which are quite pertinent to the present study are briefly discussed below.

Tautomerism of β-diketones

Since the preparation of acetylacetone and similar 1,3-dicarbonyl compounds in the later half of the 19th century, organic chemist has considerable interest in their properties, especially their ability to exhibit keto-enol tautomerism. The 1,3-diketones contain a methylene group or a substituted methylene group which is interposed between acyl or aroyl groups. Usually, 1,3-diketones exist as a mixture of keto 1 and enol 2 forms related by a 1,3-hydrogen shift.
Usually, the enolic form is favoured in nonpolar solvents and simultaneous conjugation and chelation through hydrogen bonding is responsible for the stability of the enol tautomers. The proportion of the enol tautomer is dependent on a number of factors like solvent, temperature and substituents. In general, the amount of enol form decreases when a bulky alkyl substituent is present at the $\alpha$-position. This can be attributed to the steric hindrance offered by the bulky group together with inductive effects of the alkyl groups. Presence of electron withdrawing groups such as Cl, Br, CN & CH$_3$COO at the $\alpha$-position increases the proportion of the enol tautomer. The enolization also increases when the compounds are fluorinated or contain an aromatic ring. The removal of the active hydrogen from the enol/keto forms generate the 1,3-diketonate anion.
Metal complexes of β-diketones

The coordinating abilities of 1,3-diketones were recognized as early as in 1887 when, Combes reported the synthesis of beryllium acetylacetonates.\textsuperscript{11} This was followed by the pioneering work of Werner\textsuperscript{12}, Morgan\textsuperscript{13,14} and Sidgwick\textsuperscript{15} and confirmed the bidentate chelating character of these ligands. The diketonate anion, being a powerful chelating agent, form complexes with virtually almost all the metal and metalloid ions in the periodic table. Literature on β-diketones and metal β-diketonates are so voluminous that even an attempt to summarise is purposefully avoided. However, since β-diketones can be bonded to metal ions in a variety of ways, the different coordination modes reported are briefly mentioned below.\textsuperscript{16}

In general, metal β-diketonates can be divided into four categories. (1) Oxygen bonded (2) Carbon bonded (3) Both carbon bonded and oxygen bonded and (4) Olefin bonded. Typical examples are given in structures 4-14.

1) Oxygen bonded β-diketonate complexes
2) Carbon bonded complexes

\[ \text{M} = \text{Sn(II), Se(II)} \]

3) Both carbon and oxygen bonded complexes
4) Olefin bonded complexes

Structural characterisation of metal complexes of β-diketones

Almost all the available spectral techniques as well as diffraction data along with other physical and chemical methods have been extensively employed in studying the structure and nature of bonding in various metal 1,3-diketonates.\textsuperscript{17} Thus, the uv-visible absorption spectral data together with magnetic moment values have been widely employed in establishing the structure and stereochemistry of the various metal diketonates. The importance of ir, nmr and esr spectral data in elucidating the structure and
nature of bonding in coordination compounds were in fact started with the application of these techniques in metal β-diketonates.\textsuperscript{17}

**Electronic Spectra:** Interpretation of electronic absorption spectral data in establishing the structure and nature of bonding of metal β-diketonates has been a major research activity in coordination chemistry for a long time. Thus, numerous reports exist on uv-visible spectral data of metal β-diketonates. Theoretical calculations based on SCF and LCAO-MO calculations of the various absorptions are also available, particularly in the case of metal acetylacetonates. Thus, for instance, the strong broad absorption bands appearing at \( \sim 34700 \, \text{cm}^{-1} \) and \( 49500 \, \text{cm}^{-1} \) of metal acetylacetonates have been assigned to various \( \pi-\pi^* \) transitions. Similarly, almost all the observed electronic spectral bands have been justified on the basis of various MO calculations.\textsuperscript{18-27}

**IR spectra:** Vibrational spectroscopy is one of the most important available technique for establishing the structure and nature of bonding of coordination compounds particularly metal complexes of organic ligands. This aspect of ir spectra of coordination compounds has been well illuminated from the reported ir studies on various metal β-diketonates.

Studies on the ir spectra of metal β-diketonates were initiated during the second half of the last century. Infrared spectra of metal β-diketonates
provide valuable information regarding the nature of bonding of the diketo group attached to the metal. In addition, conclusive evidence for the quasi-aromatic behaviour of the six membered $C_3O_2M$ chelate ring and various other structural features of metal $\beta$-diketonate has also been deduced from ir data. Importance of ir spectra in establishing the keto-enol tautomers of $\beta$-diketones has been well established.$^{28,29}$ For example characteristic carbonyl band of the enol form of acetylacetone appeared at 1613 cm$^{-1}$ and that of diketo form at 1725 cm$^{-1}$. Presence of a broad band at 2700-3000 cm$^{-1}$ is an indication of the intramolecularly hydrogen-bonded enol form of $\beta$-diketones.$^{30,32}$ Upon complexation, the carbonyl stretching frequency of $\beta$-diketones shows a shift (10-50 cm$^{-1}$) to lower values and additional bands due to $\nu_{M-O}$ vibrations appear in the region 400-500 cm$^{-1}$.

**NMR Spectra:** NMR spectral studies of metal $\beta$-diketonates appear to have been initiated in 1958 by Holm and Cotton$^{33}$ who assigned the positions of methyl and methine (=CH-) protons in neutral metal acetylacetonates. They observed that the chemical shifts were close to those observed for olefinic protons and were nearly independent of the size, charge and $\pi$ bonding ability of the metal ion. The position and nature of splitting of the signals depends on the mode of the coordination, nature of the substituents and the extent of delocalization in the chelate ring.$^{34-39}$ The cis enol proton chemical shift, $\delta$(OHO)/ppm, of $\beta$-diketone and $\beta$-ketoaldehyde of general formulæ
R'COCH (R") COR\(^{111}\) have been reported.\(^{40}\) Nonhebel\(^{41,42}\) showed that the bulky substituents on the \(\alpha\) and \(\beta\) sites not only shifted \(\delta(OHO)\) down field but produced a sharper line.

**X-Ray Diffraction studies:** The m-chloro and m-bromo derivatives of dibenzoyl methane were the first \(\beta\)-diketones to be investigated by X-ray methods.\(^{28,29,43}\) The crystal and molecular structures of several metal \(\beta\)-diketonates have been determined by the 3-dimensional X-ray method.

**Mass spectra:** Mass spectroscopy is an efficient tool in the structure elucidation of coordination compounds.\(^{44-46}\) Macdonald and Shammon\(^{47}\) studied mass spectra of a series of metal acetylacetonates. The most intense peaks in the spectra are usually derived from the monomeric forms of the complexes, but rarely peaks due to dimer or even trimer have also been observed. These studies confirm the influence of the odd or even electron character of an ion on its dissociation reactions (McLafferty)\(^{48}\) and provides an additional evidence\(^{44-46}\) that odd electron ions can be changed to even electron ions and vice versa, by change of valency of the metal atom in the ions.

**Thermogravimetric studies:** Thermal analysis is a well established method for the characterization of inorganic complexes. Sievers and co-workers\(^{49,50}\) have made a detailed comparative study of the thermal stability of derivatives of lanthanons with different \(\beta\)-diketones. These workers found that size and
extent of fluorination of the ligand along with careful selection of substituents attached to the donors, enhances the volatility and stability of resulting complexes.\textsuperscript{50}

**Applications and use of metal complexes of $\beta$-diketones:** The chemical reactivity coupled with volatility, thermal and solvolytic stability of metal $\beta$-diketonates have been exploited in solvent extraction studies of various ions and gas chromatographic separations of several metals. The application of certain coordinately unsaturated lanthanide chelates, called 'shift reagents' for nmr spectral elucidation has become an extremely useful analytical technique.\textsuperscript{51-54} Addition of certain metal $\beta$-diketonates for measurements of carbon-13 nmr spectra is effective in reducing the normally long longitudinal relaxation times, thus minimizing saturation effects and allowing more rapid collection of data.\textsuperscript{55-59}

The chemistry of lanthanide $\beta$-diketonates has assumed considerable importance because of their practical use as potential laser materials.\textsuperscript{60-64} Since the development of gas chromatography as an efficient technique for separation and estimation of different species, volatile compounds of metals have assumed special significance.\textsuperscript{65-69} Fluorinated $\beta$-diketones are highly useful in the solvent extraction of metals.\textsuperscript{70-74} Metal complexes of $\beta$-diketones are used as fuel additives,\textsuperscript{75} as supercritical fluids for waste clean up\textsuperscript{76} in superconducting thin film manufacturing\textsuperscript{77} and in production of homogeneous
and heterogeneous catalysts.\textsuperscript{78,79} Iron(II) and iron(III) chelates of β-diketone are used as catalysts for the removal of hydrogen sulphide from natural gas.\textsuperscript{80}

Time resolved fluorescence spectra of europium chelates of β-diketones is one of the most rapidly growing areas of application of fluorescence spectroscopy. Highly sensitive time-resolved fluorometric determination of estrogens by HPLC using europium β-diketonate are reported.\textsuperscript{81} Microsecond time-resolved fluorimetry (TRF) of europium chelates was introduced in the area of nucleic acid hybridization assays and immunoassays of proteins.\textsuperscript{82-89}

**Naturally occurring β-diketones**

Majority of the reported studies on metal β-diketonates are based on synthetic β-diketones in which, the diketo function is directly linked to alkyl/aryl groups. However active chemical components of several medicinal plants contain one or more carbonyl group as essential functional group. Many of the medicinal and other biological properties of these plants are due to the presence of these type of compounds.

Several plant species are known to exert wide range of beneficial physiological effects in addition to aroma and flavour. Even in the modern world, nature is still the greatest source of drugs and pharmaceuticals. The Indian subcontinent is endowed with rich and diverse local health traditions
which is matched with an equally rich and diverse plant genetic resources. The classical systems of medicine are also based on herbal medicine.

Herbs and herbal constituents are found to be safe and function as natural remedies for many tragic illness. Powerful antioxidants originating from edible and medicinal plants have been extensively investigated as important inhibitory materials for the prevention of oxidative deterioration of lipids. Recently it has been shown that peroxidation in living organism is closely related to the initiation of some human diseases, such as cancer, coronary heart disease and Alzheimer's disease. Ingestion of antioxidants may possibly prevent these diseases.

The state of health is a result of body's ability to recover from the continuous challenges posed by toxic substances entering through air, food and water. The most vivid example of this struggle, is our defence against chemicals that cause cancer. Most cancer causing compounds (carcinogens) undergo metabolic change in the body to 'activated' carcinogens. The 'activated' carcinogen binds to the cell DNA, and damages it forming the so called DNA adducts. Chemoprevention includes the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred.
Foods of plant origin contain many bioactive compounds in addition to vitamins and minerals. These phytochemicals belong to several classes of organic compounds such as sulphur containing compounds, terpenoids, flavanoids, polyphenols, carbonyl compounds, etc. Some of the naturally occurring carbonyl compounds and their main plant sources are given in Table 1. In addition to carbonyl group, several other functional groups are also present in these compounds.

Table 1

Active constituents of some common spices and medicinal plants

<table>
<thead>
<tr>
<th>Spice (Plant species)/ Active Principle</th>
<th>Structure</th>
</tr>
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<tbody>
<tr>
<td>Black pepper (<em>Piper nigrum</em>) piperine</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Turmeric (<em>Curcuma longa</em>) Curcuminoids</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Indonesian medicinal ginger (<em>Zingiber cassumunar</em>) Cassumunin A</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>Cassumunin B</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>Spice (Plant species)/Active Principle</td>
<td>Structure</td>
</tr>
<tr>
<td>--------------------------------------</td>
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</tr>
<tr>
<td>Cassumunin C</td>
<td><img src="image" alt="Cassumunin C Structure" /></td>
</tr>
<tr>
<td>Fruits and nuts (grapes, strawberries) Ellagic acid</td>
<td><img src="image" alt="Ellagic acid Structure" /></td>
</tr>
<tr>
<td>Terpenoids (Citrus fruits) Nomillin</td>
<td><img src="image" alt="Nomillin Structure" /></td>
</tr>
<tr>
<td>Limonin</td>
<td><img src="image" alt="Limonin Structure" /></td>
</tr>
<tr>
<td>Flavanoids and flavanones (Most vegetable fruits and cereal grains) Quercetin</td>
<td><img src="image" alt="Quercetin Structure" /></td>
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</tbody>
</table>
Among the various naturally occurring carbonyl compounds, curcuminoids possess several interesting structural features and numerous practical applications. Structurally they are typical 1,3-diketones in which diketo function directly attached to olefinic groups. Recently metal complexes of curcuminoids and several structurally related compounds have been synthesized and characterized.\textsuperscript{94-98} Since the present investigation is mainly on metal complexes of synthetic analogues of natural curcuminoids, some of the chemical and biochemical aspects of curcuminoids are briefly mentioned below.

**Chemical and biochemical aspects of curcuminoids**

The main source of curcuminoids is the herbaceous Indian medicinal plant turmeric (\textit{Curcuma longa} Linn.). Turmeric is used as a spice in Indian cooking and also as a household medicine. Its pharmacological properties are well documented in ancient Indian literature.\textsuperscript{99,100} Turmeric is a common ingredient in many traditional Indian ceremonies and cosmetic preparations. Also, turmeric occupies an important position in the life of Indian people as a common remedy for many diseases. A paste of turmeric and slaked lime is an household remedy for grains, muscular pain and inflamed joints. Turmeric powder is still used against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis.\textsuperscript{101-109}
Constitution of curcuminoids: Natural curcumin isolated from turmeric contains three well defined yellow compounds.\textsuperscript{103} In 1953, Sreenivasan \textit{et al} separated these three curcuminoids using column chromatography over silica gel.\textsuperscript{104} Later these compounds were identified.\textsuperscript{103,104} as curcumin I (diferuloyl methane) as the major component, curcumin II (feruloyl-p-hydroxy cinnamoyl methane) and curcumin III [bis-(p-hydroxy cinnamoyl methane] as in structure 15 given below.

\[
\begin{align*}
\text{Curcumin I} & : \text{OCH}_3 & \text{OCH}_3 \\
\text{II} & : \text{OCH}_3 & \text{H} \\
\text{III} & : \text{H} & \text{H}
\end{align*}
\]

The structure of the compounds were later confirmed by chemical degradation studies and by spectral techniques.\textsuperscript{108}

Synthesis of 1,7-diarylheptanoids: The synthesis of curcumin was first reported in 1913 by Lampe and Milobedzka.\textsuperscript{105} This method was further improved by Povoloni.\textsuperscript{106} H.J.J. Pabon developed a general method of synthesis for curcuminoids\textsuperscript{107} and related 1,7-diarylheptanoids in good yield. This method involve the condensation of an aromatic aldehyde and
acetylacetone in presence of $\text{B}_2\text{O}_3$, tri(sec butyl) borate and n-butylamine. The reaction was carried out in dry ethyl acetate in the temperature range 85-110°C. According to Pabon, an acetylacetone-boric oxide complex first formed prevent Knoevenagel type condensation and facilitate Claisen type reaction.

**Structure of curcuminoids:** Electronic, ir, nmr and mass spectral data of curcuminoids and a number of 1,7-diarylheptanoids have been reported.\textsuperscript{99,108} Spectral analysis established that the curcuminoids exist predominantly in the intramolecularly hydrogen bonded enol form.\textsuperscript{110} The crystal and molecular structure of curcumin 1 has been reported\textsuperscript{111} by X-ray crystallographic methods. These data will be quoted at appropriate places while discussing the results of the present investigation.

**Free radical scavenging and antioxidant efficiency of curcuminoids**

Free radicals are produced in biological systems by the ionization of water by high energy radiations,\textsuperscript{112} through metabolism, by triggered inflammatory phagocytes to reactive oxidants\textsuperscript{113} and during oxidative phosphorylation.\textsuperscript{114} These free radicals are highly reactive species, which react with biological compounds causing tissue damage. Antioxidants can counteract against this free radicals.

Curcuminoids are natural phenolic compounds, with potent antioxidant properties.\textsuperscript{115-117} Both turmeric and curcuminoids can inhibit
generation of potent free radicals like superoxide and hydroxyl radicals.\textsuperscript{118} The antioxidant properties of curcumin in prevention of lipid peroxidation, another process that generates free radicals is well recognized.\textsuperscript{119-121} The primary role of curcumin as a lipid soluble antioxidant is to intercept peroxyl free radicals formed during lipid peroxidation. This prevents free radical chain reactions which deteriorate the lipid membrane.\textsuperscript{122,123}

**Medicinal uses of turmeric and curcuminoids**

Turmeric is a traditional house hold Indian medicine.\textsuperscript{124} Certain studies revealed that the topical applications of curcuminoids in patients improve wound healing significantly and protect tissues from oxidative damage.\textsuperscript{125,126} It is used as an anthelmintic. Chemopreventive effect of turmeric against stomach and skin tumours have been studied.\textsuperscript{127-130} Turmeric has anti-mutagenic,\textsuperscript{131,132} property and prevents the DNA damage induced by smoke,\textsuperscript{133,134} and lipid peroxidation and prevent BP-DNA adduct formation.\textsuperscript{135} Studies have shown that many of the biological properties of turmeric are due to the presence of the curcuminoids.\textsuperscript{111,136-147}

The pharmacological studies revealed that synthetic curcuminoids also have antimicrobial, antiinflammatory and anticarcinogenic activities.\textsuperscript{137,138,148-163} Curcuminoids inhibits 4-nitroquinoline-1-oxide induced oral carcinogenesis,\textsuperscript{164} azoxymethane induced small and large intestinal carcinogenesis\textsuperscript{143} and azoxy methane induced colon carcinogenesis.\textsuperscript{165}
Antimutagenic and anticarcinogenic activity of natural and several synthetic curcuminoids have been studied.\textsuperscript{166} Antitumour and free radical scavenging activity of some synthetic curcuminoids were analysed and reported.\textsuperscript{96-98,167}

Turmeric and curcuminoids can exert protection either directly, by shielding the biomolecules, or indirectly by stimulating the natural detoxification and defence mechanisms of the body.\textsuperscript{142,168,169} Curcuminoids also play a role in protecting some drugs from physico-chemical degradation.\textsuperscript{115} Addition of curcumin to the cardiovascular drug nifedipine, prevented degradation of nifedipine due to uv light.\textsuperscript{170}

One of the important protective mechanisms of turmeric extract and the curcuminoids is against side effects produced by drug therapy. A potential preventive role of curcumin on DNA adduct formation with the carcinogen has been studied in vitro.\textsuperscript{171} Additionally, \textit{in vivo} studies on rats were also performed. As compared to the control animals, rats fed with curcumin showed decrease in levels of DNA adduct in the liver cells.\textsuperscript{172} This decrease could be explained by the competitive binding of curcumin to the active site of benzopyrene, preventing cellular DNA adduct formation.

Because of the cytotoxic nature, anticancer drugs do not discriminate between cancer cells and normal cells, and could cause damage to non-cancerous tissue as well.\textsuperscript{173} Curcumin administered to mice along with anticancer drug, cyclophosphamide, increased the life span of animals and
Curcuminoids, by virtue of their antioxidant activity, scavenge free radicals as well as prevent their formation, thereby eliminating the toxic effects of the drug.

The effect of combining curcumin with cisplatin was evaluated. Clinical use of cisplatin is limited because of its severe toxicity leading to kidney failure. Studies showed that curcumin administered to mice along with the drug decreased the side effects of the drug therapy. Additionally kidney lipid peroxidation was reduced. Curcumin inhibited the H$_2$O$_2$ and nitrite induced lipid peroxidation and haemolysis of erythrocytes \textit{in vitro}. \cite{176,177}

The hepatoprotective action of an alcoholic extract of curcumin against CCl$_4$-induced liver injury \textit{in vitro} \cite{178} and \textit{in vivo} \cite{179} was tested. Curcumin significantly reduced the urinary excretion of tobacco mutagens, and also enhanced the activity of enzymes to detoxify cigarette smoke mutagens and carcinogens. \cite{180,181} Curcumin also inhibits \textit{in vitro} production of aflatoxins which causes injury to the liver. \cite{182,183} Probably one of most discussed properties of curcuminoids is their anti-HIV effect demonstrated during \textit{in vitro} and \textit{in vivo} experiments, including a limited number of human studies. \cite{184,185} Important beneficial physiological activities of turmeric and curcuminoids are listed in table 2.
### TABLE 2

**Important biological activities of Turmeric (Curcuminoids)**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Biological Activity</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Antiinflammatory</td>
<td>102, 140, 136, 144, 148, 149, 150,</td>
</tr>
<tr>
<td>2</td>
<td>Antiarthritic</td>
<td>105, 151</td>
</tr>
<tr>
<td>3</td>
<td>Antispasmodic</td>
<td>152, 153, 154, 155, 163</td>
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<tr>
<td>4</td>
<td>Antiepatoxotoxic</td>
<td>154, 163</td>
</tr>
<tr>
<td>5</td>
<td>Antiulcerogenic</td>
<td>143</td>
</tr>
<tr>
<td>6</td>
<td>Anticoagulant</td>
<td>156, 157</td>
</tr>
<tr>
<td>7</td>
<td>Antiprotozoal</td>
<td>158</td>
</tr>
<tr>
<td>8</td>
<td>Antifertility</td>
<td>159</td>
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<tr>
<td>9</td>
<td>Antitumour</td>
<td>123, 129, 141, 145, 146, 147, 167</td>
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<tr>
<td>10</td>
<td>Antioxidant</td>
<td>119, 121, 160, 161</td>
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<tr>
<td>11</td>
<td>Antimutagenic</td>
<td>131, 132</td>
</tr>
<tr>
<td>12</td>
<td>Wound healing</td>
<td>162</td>
</tr>
<tr>
<td>13</td>
<td>Hypotensive</td>
<td>163</td>
</tr>
</tbody>
</table>

### Metabolism of curcuminoids

The metabolic fate of curcuminoids has not been examined in detail though it is of relevance in view of their use as a food ingredient and as a medicine. Reports on the uptake, distribution and excretion of curcumin in rats have appeared only recently.\textsuperscript{186-190} However, it is to be pointed out that the results obtained are contradictory. Wahlstrom and Blennow\textsuperscript{186} observed that 65-85% of the oral administered dose of curcumin was excreted in the faeces, while negligible amounts were recovered in the urine.
Measurements of plasma levels and biliary excretion in anesthesised animals given curcumin revealed a very low absorption of curcumin into the blood. The concentration of curcumin in the bile, liver, kidneys and body fat was negligible and the major part of the administered curcumin was found in the intestine. After intravenous injection, curcumin disappeared rapidly from the blood and excreted in the bile. Addition of curcumin to liver perfusion systems and isolated hepatocytes and liver microsomes showed that the sample was quickly metabolised and do not retain in the body over a prolonged period. This led to the conclusion that the liver was the major site of curcumin metabolism.

Holder and co-workers reported that following an oral dose, more than 90% of the dose was excreted in faeces as glucoronide conjugates of tetrahydrocurcumin (50%), hexahydrocurcumin (42%) and dihydroferulic acid. The recovery in urine was only 6%. This again indicated that curcumin and its metabolites were undergoing biliary excretion.

Ravindranath and Chandrasekhara studied the in vitro absorption of curcumin using everted intestinal sacs and found that 30 to 80% of the added sample disappeared from the mucosal side of the sacs whereas in vivo studies indicated that nearly 40% of the curcumin dose was excreted unchanged in the faeces and curcumin could not be detected in the urine, blood, liver or kidney.
Based on the reported works,\textsuperscript{187-190} it is difficult to draw any conclusion about the fate of curcumin \textit{in vivo}. After oral administration in rats, it seems likely that curcumin to a certain extent is metabolised in the liver and its metabolites are mainly excreted \textit{via} the bile and the faeces. The amount of curcumin dose that is excreted unchanged and the exact metabolites of curcumin are not fully established.\textsuperscript{99,100}

\textbf{Toxicological studies on curcuminooids}

Turmeric and curcuminooids are present in most habitual Indian diets as a part of the spices used in the traditional cooking and no ill effects have been observed. However, the FAO/WHO Expert Group did recommend that turmeric and curcuminooids should be properly evaluated when listed as a permitted food colourant. A temporary average daily intake (ADI) of 2.5 mg/kg body weight is set for turmeric.

Acute toxicity studies on turmeric in animals indicated no toxic effects of the drug even at high doses.\textsuperscript{192-194} Further, short- and long-term studies in dogs, mice and rats did not reveal any adverse cytogenic and mutagenic effects compared with controls when curcumin was incorporated into the diets in amounts normally consumed by man.\textsuperscript{195} Some attention has been given to mutagenicity studies recently and curcumin itself exhibited no mutagenic effects in the salmonella/mammalian microsome test.\textsuperscript{190} The above studies thus indicate that both turmeric and curcuminooids are toxicologically safe even in doses far beyond the ADI given by FAO/WHO.\textsuperscript{196}
Metal complexes of curcuminoids

In a typical Hindu religions ceremony, turmeric is mixed with Ca(OH)$_2$ and rice. In this process the natural yellow colour of turmeric turns to a deep red colour. The colour change may be due to the interaction of curcuminoids with calcium ions. The Ca$^{2+}$ ions may replace either enolic/phenolic proton, and changes the chromophoric group. A gold(I) complex of curcumin 1 was reported to possess antiarthritic activity. Recently synthesis and characterization of stable Cu$^{2+}$, Ni$^{2+}$, Co$^{2+}$, Zn$^{2+}$ and Pd$^{2+}$ complexes of some synthetic curcuminoids were appeared in the literature. Antitumour studies of metal chelates of these synthetic curcuminoids were also reported.

Importance of the present investigation

Coordination chemistry of biologically important plant products have gained considerable importance in recent years. This is evident from the numerous reports on medicinal and other aspects of curcuminoids and allied derivatives. However metal complexes of curcuminoids have not received as much attention as they deserve. The present investigation is mainly on the synthesis and characterisation of metal complexes of a series of synthetic curcuminoid analogues. The antioxidant and cytotoxic activities of these curcuminoids and their metal complexes were also studied in detail.