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Enhanced Stability and Bioavailability of Curcumin through Titanium Complexation: Synthesis and Characterization

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Abstract

Curcumin, the active compound derived from turmeric, is recognized for its diverse pharmacological properties, including anti-inflammatory, antioxidant, wound-healing, hypoglycemic, and antimicrobial activities[3]. However, its clinical application is constrained by physicochemical limitations such as hydrophobicity, poor water solubility, low bioavailability, and rapid metabolic degradation. To overcome these challenges and optimize curcumin's therapeutic effectiveness, curcumin-metal complexes have gained significant interest. In this study, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) was successfully extracted from turmeric and subsequently complexed with titanium to improve stability and bioavailability. The titanium-curcumin complexes were characterized using infrared (IR) and UV-visible (UV-vis) spectroscopy to elucidate their structural and functional properties. Spectroscopic analysis confirmed that curcumin forms a bidentate complex with titanium ions, binding through two deprotonated functional groups. This coordination enhances curcumin's stability and bioavailability, suggesting potential for more effective curcumin-based therapeutic applications.

*Keyword: Curcumin-metal; Curcumin Titanium complex, **b**ioavailability*

1. Introduction

Curcumin, a key bioactive compound derived from the turmeric rhizome, has garnered significant attention for its diverse pharmacological effects. Known for its broad spectrum of activities, curcumin exhibits anti-inflammatory, antioxidant, hypoglycemic, antimicrobial, neuroprotective, and immunomodulatory properties. Additionally, it has been shown to be effective in treating various conditions such as anorexia, cough, colds, liver disorders, and sinusitis **(1, 2).** Curcumin commonly interacts with metals via its β-diketone group, forming stable metal–curcumin complexes.

Recent studies have demonstrated that curcumin forms strong chelation bonds with several metal ions, including boron, cobalt, copper, gold, lanthanum, manganese, nickel, iron, palladium, platinum, ruthenium, silver, vanadium, titanium, and zinc. The formation of these metal–curcumin complexes enhance curcumin's solubility, cellular uptake, and bioavailability, amplifying its therapeutic effects, particularly in antioxidant, anti-inflammatory, antimicrobial, and antiviral applications. Notably, metal–curcumin complexes have shown promise in combating chronic illnesses, including cancer, arthritis, osteoporosis, and neurological disorders like Alzheimer's disease.

The therapeutic efficacy of these metal–curcumin complexes is attributed to their ability to modulate key biological pathways and molecules, such as inflammatory mediators, transcription factors, protein kinases, antiapoptotic proteins, lipid peroxidation processes, and antioxidant enzymes. Beyond their medicinal applications, metal–curcumin complexes are also valuable in biological and radiological imaging, offering potential advancements in diagnostic imaging techniques.

In summary, the formation of curcumin-metal complexes might be an option that presents a promising strategy for overcoming curcumin's intrinsic limitations while enhancing its therapeutic efficacy and expanding its biomedical applications. These complexes serve as a bridge between traditional medicine and modern biochemical engineering, opening pathways for new treatments and diagnostic tools in a range of clinical and industrial contexts.

2. Curcumin chemical structures

Curcumin is a beta-diketone compound in which two hydrogens are substituted by feruloyl groups. It exists in two primary tautomeric forms: keto and enol. The keto form is stable in acidic and neutral pH environments, while the enol form predominates in alkaline conditions **(4).** Structurally, curcumin features a seven-carbon linker and three key functional groups: an α, β-unsaturated β-diketone structure, an O-methoxy-phenolic aromatic group, and the seven-carbon linker itself, as illustrated in Fig 1A. The molecule's two α, β-unsaturated carbonyl groups link its aromatic rings.

These diketones can easily undergo deprotonation to form enolates, as shown in Fig 1B, while the α, β-unsaturated carbonyl group serves as a Michael acceptor, facilitating nucleophilic addition reactions **(5).** The antioxidant properties of curcumin are attributed to its phenolic group, while the seven-carbon linker contributes hydrophobic characteristics, enhancing its stability and reactivity, as illustrated in Fig 1C **(6).**

Studies have shown that the carbonyl group within curcumin's β-diketone moiety is destabilized upon coordination with metal ions **(7).** Given that metals often serve as enzyme coactivators, curcumin–metal complexes can engage with enzyme active sites, thereby initiating a range of cellular processes. Typically, metals bind to curcumin's β-diketone moiety via chelation—a chemical bonding process that involves forming dative covalent bonds (also called coordinate bonds) between a metal cation and at least one multidentate ligand. Unlike traditional covalent bonds where both atoms contribute electrons, dative bonds rely on electrons donated solely by one atom, lending the bond a semi-polar character. This chelation interaction leads to structural modifications in curcumin. Generally, metals form chelation bonds with either one or two curcumin molecules.

The metal coordination primarily occurs through curcumin's enolic group, where the enolic proton is substituted by a metal ion (Figure 1D), while the o-methoxy phenolic group remains unaffected in the complex. When a single curcumin molecule binds to a metal ion in a 1:1 ratio, it induces variations in all four metal-oxygen (metal–O) bond lengths within the complex. In contrast, in a 1:2 metal–curcumin complex, the metal–O bond lengths are identical. The 1:1 metal–curcumin complex tends to display orthorhombic symmetry, whereas a 1:2 complex exhibits a square planar arrangement around the metal ion. Additionally, in the 1:2 metal–curcumin complex, steric repulsion has been observed between the methoxy groups on the phenolic rings of the two curcumin molecules **(9).**

Curcumin–metal complexes have been successfully synthesized with various transition and non-transition metal ions, rare earth elements, and metal oxides **(11).** Forming these complexes not only alters curcumin's physical and chemical attributes but also modulates the biological reactivity of the metals involved. Interestingly, curcumin–metal complexes tend to mitigate the toxicity of the metal ions, thereby enhancing their therapeutic potential **(5).**

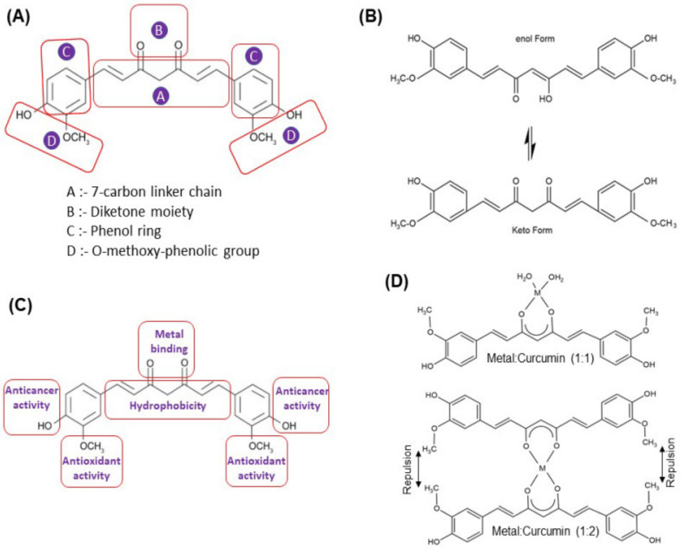

Figure 1 (A) The Curcumin chemical structure. (B) The keto-enol tautomeric forms of Curcumin. (C) the functional groups of curcumin responsible for its biological activities. (D) Structure of 1:1 or 1:2 Curcumin-Metal complexes showing the β-diketone moiety of curcuminoid as the metal binding site.

3. Materials and methods

3.1 Synthesis of the Curcumin–Metal Complexes

To synthesize a curcumin–metal complex, both curcumin and the metal need to be in solution form to facilitate the reaction. However, due to curcumin's low solubility in water, it must be dissolved using organic solvents to achieve the desired reaction conditions. Commonly used solvents for this purpose include methanol, ethanol, and acetone, which effectively dissolve curcumin and prepare it for coordination with metal ions.

In contrast, the metal ions involved in forming the complex are typically introduced as metal salts, which readily dissolve in aqueous solutions, ensuring a uniform distribution of metal ions. This dual-solution setup—organic solvents for curcumin and aqueous media for metal salts—enables the reaction to proceed efficiently, allowing curcumin to interact with the metal ions and form a stable complex.

3.2 Purifications and Extracting of Curcumin

To extract curcumin from turmeric, 80 grams of ground turmeric was dissolved in 200 mL of dichloromethane. This solution was then subjected to magnetic stirring and heated under reflux for 2 hours to promote effective extraction. Following this, the mixture was filtered under suction to remove any solid impurities. The resulting filtrate was concentrated by heating in a hot-water bath maintained at 60°C, leading to the formation of a reddish-yellow oily residue.

To further purify the extract, the oily residue was triturated with 80 mL of hexane, inducing the formation of a solid, which was then collected by suction filtration. This crude solid was dissolved in a minimal amount of a solvent mixture composed of 99% dichloromethane and 1% methanol, preparing it for column chromatography. The sample was loaded onto a column packed with 30 grams of silica gel and subsequently eluted with the same dichloromethane–methanol solvent mixture.

Thin-layer chromatography (TLC) analysis of the collected fractions revealed three distinct components. The fractions containing the least polar, colored component were pooled, and the solvent was evaporated in a hot-water bath, yielding a pure yellow solid. This final product had a yield of 72% and a melting point in the range of 182-184°C, indicating high purity.

3.3 Preparation of Titanium – Curcumin complex

Titanium tetrachloride salt was combined with curcumin in a 4:1 molar ratio (titanium ion to curcumin) and manually ground in a mortar until a uniform powder was formed. Following this, a solution of propylene glycol and water (1:1 v/v) was added to the mixture, and the combination was shaken mechanically at 25°C. This process continued until a paste-like consistency developed, indicating successful interaction between the components.

The pasty mixture was then subjected to drying at 60°C, resulting in the formation of powdered titanium-curcumin complexes. To ensure purity, these powdered complexes underwent further purification through silica gel column chromatography (G60 grade), effectively isolating the desired product from any impurities.

4. Results and discussions

4.1 Structural analysis techniques for Ti-Curcumin Complex

- UV-vis spectroscopy
- Fourier transform infrared

They all have been implemented to determine the binding of metals to the curcumin.

4.2 UV-Vis spectra

The comparative electronic absorption spectra of curcumin and its Titanium complex are displayed in Fig. 2. Curcumin itself exhibits a primary absorption band attributed to a π-π* transition within the 415–430 nm range. Upon complexation with the Titanium ions, the maximum absorption of these Curcumin-Titanium complexes is shifted slightly (by 2–8 nm), suggesting that the carbonyl group of curcumin participates actively in bonding with the Titanium ions. Additionally, the appearance of shoulder peaks at 410–414 nm and 449–454 nm is associated with a charge-transfer interaction between curcumin and titanium ions, forming a specific curcumin-titanium complex (12).

It is suggested that the shifts in curcumin's primary absorption peak and the variations in the shoulder peaks across different complexes are influenced by the properties of the titanium ion itself. A detailed summary of these spectral observations can be found in Table 1. Furthermore, the UV spectrum of the titanium-curcumin complex in acetone Fig. 3 reveals a notable absorption maximum at 419 nm, corresponding to a π-π* transition that is shifted to a shorter wavelength compared to free curcumin.

A distinctive feature of the spectra is the presence of three weaker absorption bands at 586 nm, 610 nm, and 634 nm, which are associated with the f-f transitions of the Titanium-curcumin complex, specifically assigned as 7F1→5D1, 7F1→5D0 and 7F2→5D0 . These transitions further substantiate the formation of the curcumin-titanium complex, as illustrated in Fig.4.

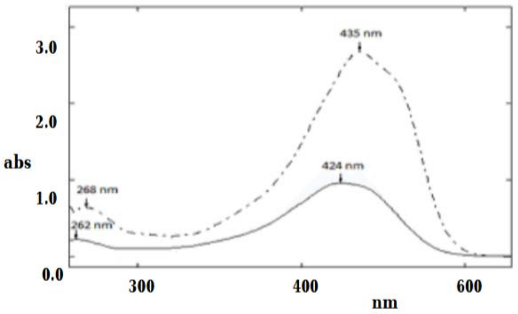

Figure 2 shows UV-Vis spectra of curcumin (─) and its Ti-complex (--)

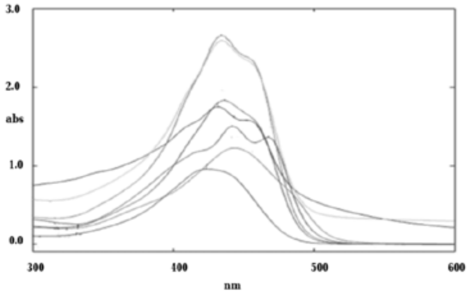

Figure 3 shows UV-visible spectra of curcumin and its Ti-complex in inorganic solvents

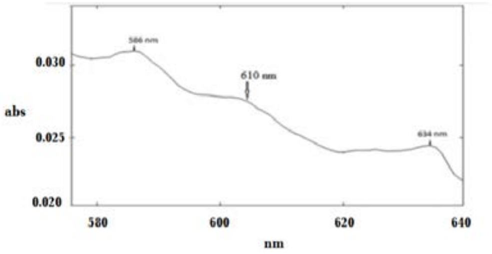

Figure 4 shows UV-Vis spectra of Ti-Curcumin complex in acetone

Table 1. UV-Vis Spectra data of curcumin and its Titanium complex. Compound UV-Vis (nm) peaks Curcumin.

Sample type	UV-Vis (nm) peaks		
Curcumin	436 (λmax)	-	266
Ti-Curcumin complex	449 (λmax)	478	374

4.3 FT-IR spectrum of curcumin

The IR spectrum of curcumin, as shown in Fig. 5 and summarized in Table 2, reveals several key absorption peaks characteristic of its molecular structure. A sharp peak at 3512 cm^{-1} corresponds to the stretching of the phenolic O-H group, accompanied by a broad band ranging from 3200–3500 cm^{-1}, indicative of the ν(OH) group in the enol form. Additionally, low-intensity bands observed between 3079–3000 cm^{-1} are assigned to the aromatic ν(C-H) vibrations, while lower frequency bands represent the motions of methyl groups.

Significant absorption bands at 1629 and 1603 cm^{-1} are attributed to mixed stretching vibrations of ν(C=C) and ν(C=O) bonds within the curcumin structure. The most prominent peak in the IR spectrum appears at 1510 cm^{-1}, which is associated with complex, highly mixed vibrations involving ν(C=O), δ(CCC), δ(CC=O), and aromatic ν(CC) and ν(CCH) stretching. Pure deformation vibrations of the methyl groups are observed at 1460–1430 cm^{-1}, while most bands in the 1450–1300 cm^{-1} region display highly mixed characteristics. At 1282 cm^{-1}, a band corresponding to the pure in-plane C-H vibrations of the aromatic rings is observed. The range between 1235–1118 cm^{-1} is associated with the in-plane deformation vibrations of phenyl rings and skeletal in-plane deformations. Additionally, a distinct band at 886 cm^{-1}, attributed to the out-of-plane C-H vibration of aromatic rings, represents a relatively pure vibration. The IR bands around 856 cm^{-1} reflect highly mixed γ(C-H) and aromatic γ(CCH) vibrations, while the out-of-plane vibrations of both –OH groups are identified at 438 cm^{-1} (15, 17).

The IR spectra of curcumin and curcumin-titanium complex exhibit similar features, although they differ distinctly from that of the free curcumin ligand. A representative IR spectral lines for Curcumin and Ti-Curcumin complex are shown in Fig. 5 and Fig.6 respectively, with detailed spectral information provided in Table 2. Key features in the solid-state IR spectra of these complexes include characteristic bands for O-H stretching, C-H stretching, C=O stretching, C=C stretching, C-O stretching in both methoxy (OCH_3) and phenolic groups, and C-H stretching in the aromatic rings.

Notably, upon complexation, the C=O stretching bands of the curcumin ligand shift to lower frequencies, indicative of coordination with the metal ions. For instance, the IR spectrum of free curcumin shows a ν(C=O) band at 1628 cm^{-1} and a ν(C=C) band at 1604 cm^{-1}. In the Titanium curcumin complex, both bands are shifted to lower energies, which is consistent with the involvement of the C=O group in binding to the metal center. Additionally, a broad band observed between 3200–3600 cm^{-1} suggests the presence of water molecules within the complex structure.

Further supporting evidence for Titanium-ligand bonding is provided by the appearance of new band in the 522 cm^{-1} , which correspond to the formation of M-O bonds. This shift and the new bands strongly indicate that curcumin coordinates with the central metal ions via the C=O group, stabilizing the complex (6, 15, 1).

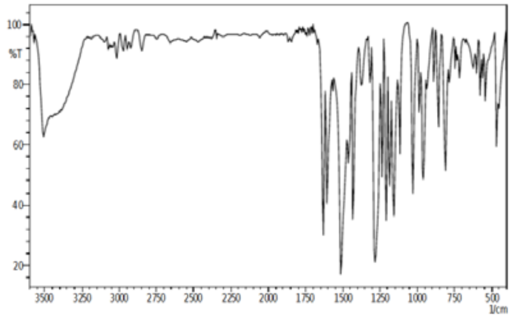

Figure 5 shows FTIR spectrum of curcumin

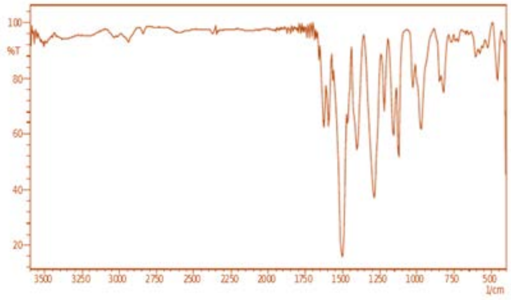

Figure 6 shows FTIR spectra of Ti-Curcumin complex

Table 2

Sample type	**UV-Vis (nm) peaks**			
	ν(O-H)	ν(C=O)	ν(C=C)	ν(M-O)
Curcumin	3512, 3200-3500	1628	1604, 1511	
Ti-Curcumin complex	3200-3600	1622	1589, 1501	522

4.Conclusion

Curcumin was obtained through extraction from turmeric and additionally synthesized via the condensation reaction between vanillin and acetyl acetone. A comparative analysis using UV-Visible and FTIR spectroscopy confirmed the structural integrity of the synthetic curcumin, aligning it with the natural form. Subsequently, Ti-Curcumin complexes were synthesized from this curcumin ligand. The formation of these complexes was validated through UV-Visible and FTIR spectroscopic techniques, providing confirmation of their successful synthesis and structural properties.

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